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Evaluation of iron deficiency anemia during acute infection in children

Yunus Nas[1,2], Abdulkadir Bozaykut[3]

[1]*Department of Child Health and Diseases, Hisar Hospital Intercontinental, İstanbul, Turkiye*
[2]*Department of Nursing, School of Health Sciences, Doğuş University, İstanbul, Turkiye*
[3]*Department of Child Health and Diseases, Zeynep Kamil Women's and Children's Diseases Training and Researches Hospital, İstanbul, Turkiye*

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ABSTRACT

Aims: The purpose of this study was to assess changes in infection and iron parameters during infection and at least 4-6 weeks after recovery in children diagnosed with infections, to investigate the impact of infection on iron metabolism and to determine the prevalence of iron deficiency anemia (IDA).

Methods: In this study, 151 patients who presented with fever, were diagnosed with an infection as the source of the fever, had no prior anemia investigations or antianemic treatment, and had no history of recurrent infections or chronic diseases, between September 2005 and October 2005 were included. In addition to specific tests focused on the site of infection, complete blood count, serum iron, serum total iron-binding capacity (TIBC), ferritin, C-reactive protein (CRP), transferrin saturation, and peripheral smear levels were measured at the time of admission and 4-6 weeks after follow-up.

Results: The mean age of the patients was 4.5±3.2 years, and 57.6% (n=87) of them were male. During the infection, 12% of the cases (n=18) showed iron deficiency, and 53% (n=80) were diagnosed with IDA. After infection, iron deficiency was identified in 5% of the cases (n=7), while IDA was present in 37.1% of the cases (n=50). A significant decrease in both iron deficiency (12% vs. 5%, p=0.001) and IDA (53.0% vs. 37.1%, p=0.001) ratios was observed after the infection. The group with IDA showed a larger decrease in leukocyte and CRP levels compared to the group without IDA, alongside a more marked increase in TIBC levels.

Conclusion: The reduction in iron deficiency and IDA rates following infection suggests that infection may lead to substantial changes in iron metabolism. Monitoring iron parameters during the infection phase in pediatric patients may play a crucial role in distinguishing anemia of inflammation from IDA.

Keywords: Anemia, ferritin, infection, iron deficiency anemia, total iron-binding capacity

INTRODUCTION

Iron deficiency anemia (IDA) remains one of the most common in developing countries.[1] It is characterized by a decrease in hemoglobin concentration due to insufficient iron, leading to impaired oxygen transport.[2] The pediatric population is particularly vulnerable to the effects of iron deficiency, which can have long-term consequences on cognitive development, growth, and overall health.[3]

Acute infections, frequently encountered in pediatric care, may complicate the diagnosis and management of IDA.[4] During an infection, inflammatory processes can alter iron metabolism, leading to a reduction in serum iron levels and changes in the hematological profile.[5,6] This phenomenon, known as anemia of inflammation (AI), shares several overlapping features with IDA, complicating the differentiation between these two conditions.[7,8]

Understanding the interaction between acute infections and iron deficiency in children is crucial for timely and effective management. Acute infections can mask or exacerbate pre-existing iron deficiency, leading to delayed treatment or inappropriate interventions.[9-11] Furthermore, anemia may worsen the course of infection, potentially prolonging recovery time and increasing susceptibility to further health complications.[12,13]

The purpose of this study was to assess changes in infection and iron parameters during infection and at least 4-6 weeks after recovery in children diagnosed with infections, to investigate the impact of infection on iron metabolism and to determine the prevalence of IDA.

Corresponding Author: Yunus Nas, dryunusnas@gmail.com

METHODS

Following the principles set forth in the Declaration of Helsinki, this prospective study was conducted at the Zeynep Kamil Women and Children's Diseases Training and Researches Hospital Child Health and Diseases Polyclinic from September 2005-October 2005. This study was produced in the thesis study conducted in 2006. Informed consent was obtained from all participants.

The study included 151 patients, aged 6 months to 13 years, who presented with fever, were diagnosed with an infection as the cause of the fever, had not been previously investigated for anemia or received any antianemic treatment, and had no history of frequent infections or chronic disease. At the initial evaluation, all patients underwent a Direct Coombs test and reticulocyte count to rule out hemolytic disease. In addition to specific tests focused on the site of infection, complete blood count, serum iron, serum total iron-binding capacity (TIBC), ferritin, C-reactive protein (CRP), transferrin saturation, and peripheral smear levels were measured at the time of admission and 4-6 weeks after follow-up.

The complete blood count and reticulocyte count were automatically measured within 90 minutes using the Beckman Coulter Gen-S device, after drawing 2 cc of blood into a K3 EDTA tube. The direct Coombs test was conducted with the Diamed-ID Micro Typing System kit (DiaMed AG, Morat, Switzerland). For the peripheral smear, a blood smear prepared from the fingertip was air-dried and stained with May Grünwald stain for 3 minutes. After removing excess stain with distilled water, it was stained with Giemsa for 8 minutes. The remaining stain was rinsed off with water, and the smear was air-dried again. The prepared smear was examined at 100x magnification with an immersion objective, and anisocytosis, hypochromia, and microcytosis were assessed. CRP values were determined by the immunonephelometric method on the BN Pro Spec device (Dade Behring, Derfield, IL, USA) using the Dade Behring kit. Ferritin levels were analyzed with the chemiluminescent immunometric method on the IMMULITE 2000 device (Diagnostic Products Corporation, LA, USA). Transferrin saturation was determined by the following formula using serum iron and total iron-binding capacity =(Serum iron / Serum TIBC)×100.

Iron deficiency was characterized by the presence of at least two of these criteria: serum iron levels below 50 µg/dl, serum ferritin below 15 ng/ml, or transferrin saturation below 12%. In addition to these criteria, patients with hemoglobin levels ≤11.5 g/dl were classified as having IDA.[14,15]

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean and standard deviation (SD) values while non-normally distributed variables are given as median (min-max). Paired sample T test, Wilcoxon signed-rank test, and mixed model for repeated measures (MMRM) analysis was performed for comparison of the post- infections laboratory findings; $p<0.05$ was considered statistically significant.

RESULTS

The study included 151 cases, comprising 87 boys (57.6%) and 64 girls, with a mean age of 4.5±3.2 years. All cases showed normal reticulocyte counts and negative direct Coombs tests. The distribution of infections was as follows: 31.1% of cases involved upper respiratory tract infections (URTIs), 18.5% involved lower respiratory tract infections (LRTIs), 17.9% involved cryptic tonsillitis, 16.6% involved acute gastroenteritis, and 15.9% involved urinary tract infections (UTIs). During the infection, 12% of the cases (n=18) showed iron deficiency, and 53% (n=80) were diagnosed with IDA. After infection, iron deficiency was identified in 5% of the cases (n=7), while IDA was present in 37.1% of the cases (n=50). A significant decrease in both iron deficiency (12% vs. 5%, p=0.001) and IDA (53.0% vs. 37.1%, p=0.001) ratios was observed after the infection. The changes in laboratory findings during and after infection are detailed in Table 1.

Table 1. Variations in laboratory findings before and after infection

Variables	During infection n=151	After infection n=151	p
Hemoglobin, g/dl	11.2±1.9	11.6±1.7	0.043*
Hematocrit, %	32.9±4.6	34.4±4	0.001*
RBC, %	4.6±0.5	4.6±0.4	0.001*
MCV, fL	72.0±9.0	73.8±8.6	0.001*
MCH, pq	24.5±3.7	24.6±3.7	0.245
MCHC, g/dl	33.9±1.7	34±1.6	0.204
RDW, %	15.7±3.9	15.7±3.7	0.398
Leukocytes, mm^3	10300 (4500-27500)	8600 (4900-13800)	0.001*
CRP, mg/L	8.1 (3.1-197)	3.2 (3.1-3.5)	0.001*
Serum iron, µg/dl	37 (3-99)	58 (11-99)	0.001*
TIBC, µg/dl	387.8±77.9	417.3±68.9	0.001*
Ferritin, ng/ml	30 (1.3-226)	17.3 (0.5-439)	0.001*
Transferrin saturation, %	10 (1-32)	14 (3-29)	0.001*
Iron deficiency, n (%)	18 (12.0)	7 (5.0)	0.001*
IDA, n (%)	80 (53.0)	56 (37.1)	0.001*

Numerical variables were shown as mean ± standard deviation or median (min-max). For numerical data showing normal distribution, the paired sample t-test was performed, while the Wilcoxon signed-rank test was used for those without a normal distribution. * p-value < 0.05 indicates statistical significance. Abbreviations: CRP: C-reactive protein, IDA: Iron deficiency anemia, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, TIBC: Total iron-binding capacity.

Table 2 presents the changes in laboratory findings for those with and without IDA after the infection. Hemoglobin, hematocrit, erythrocytes, serum iron, TIBC, ferritin, and transferrin saturation levels increased in both groups, whereas significant decreases were observed in leukocyte and CRP levels. The group with IDA showed a larger decrease in leukocyte and CRP levels compared to the group without IDA, alongside a more marked increase in TIBC levels.

DISCUSSION

In this study, we investigated the impact of acute infections on iron metabolism in pediatric patients, focusing specifically on iron deficiency and IDA. Our results show significant changes in iron parameters post-infection compared to during the infection, highlighting the dynamic relationship between infection and iron status. After infection, serum iron, TIBC, and transferrin saturation increased, while ferritin levels decreased. These observations are crucial, as they reflect the dynamic nature of iron homeostasis during the recovery phase of infection.

Table 2. The changes in laboratory findings during and after infection by presence of iron deficiency anemia after infection

Variables	IDA (-)			IDA (+)			
	During infection n=95	After infection n=95	p	During infection n=56	After infection n=56	p	Δp
Hemoglobin, g/dl	12.3±0.9	12.6±0.8	<0.001*	9.3±1.5	9.8±1.4	<0.001*	0.207
Hematocrit, %	35.5±2.5	36.7±2.1	<0.001*	28.5±4	30.6±3.5	<0.001*	0.094
RBC, %	4.6±0.4	4.7±0.4	<0.001*	4.4±0.6	4.5±0.5	<0.001*	0.305
MCV, fL	76.7±5.3	78.4±4.8	<0.001*	64±8.3	65.9±7.8	<0.001*	0.614
MCH, pq	26.4±2.1	26.5±2.2	0.542	21.4±3.8	21.5±3.6	0.168	0.705
MCHC, g/dl	34.5±0.8	34.6±0.8	0.102	32.9±2.3	33±2	0.779	0.487
RDW, %	13.9±1.3	14.0±1.1	0.136	18.7±4.9	18.6±4.7	0.531	0.097
Leukocytes, mm^3	9800 (4700-21000)	8600 (4900-13200)	<0.001*	11400 (4500-27500)	8750 (4900-13800)	<0.001*	0.037*
CRP, mg/L	6.1 (3.1-167)	3.3 (3.1-3.8)	<0.001*	10.1 (3.1-197)	3.2(3.1-3.5)	<0.001*	0.025*
Serum iron, µg/dl	50.8±26.9	64.8±17.7	<0.001*	22.5±16.4	33.7±14.5	<0.001*	0.216
TIBC, µg/dL	382.2±70.5	402.3±65.1	<0.001*	397.4±88.9	442.8±68.3	<0.001*	<0.001*
Ferritin, ng/ml	32.5(1.3-123)	21.3 (9-439)	<0.001*	22.1 (1.5-226)	9.8 (0.5-65.2)	<0.001*	0.077
Transferrin saturation, %	14 (1-32)	17 (10-29)	<0.001*	4 (1-22)	7 (3-20)	<0.001*	0.097

Numerical variables were shown as mean±standard deviation or median (min-max). For within-group temporal comparisons, paired sample t-tests were performed for numerical data with normal distribution, while the Wilcoxon signed-rank test was used for non-normally distributed data. Temporal changes between groups (Δ) were analyzed using a mixed model for repeated measures. * p-value <0.05 indicates statistical significance. Δp=Comparison of the changes of follow-ups between the groups with and without IDA. Abbreviations: CRP: C-reactive protein, IDA: Iron deficiency anemia, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, TIBC: Total iron-binding capacity.

Iron plays a dual role during infections. On one hand, it is essential for immune cell proliferation and function, particularly for T cells and macrophages. On the other hand, many pathogens, such as *Escherichia coli* and *Salmonella*, require iron for growth, making excess iron potentially harmful by fostering bacterial proliferation.[16,17] This dual role underscores the body's tight regulation of iron during infections, where limiting iron availability helps to control pathogen growth. The reduction in ferritin levels post-infection reflects the body's shift away from this defensive iron-sequestration strategy. Ferritin, an acute-phase reactant, tends to rise during infection as part of the body's defense mechanism to limit iron availability to pathogens. This phenomenon is driven by the action of hepcidin, which restricts iron release from storage sites by inducing the internalization of ferroportin, the main iron-exporting protein.[18-20] Consequently, serum iron levels drop during infection, contributing to what is known as AI. Once the infection resolves, hepcidin levels decrease, allowing iron to be mobilized from storage, which explains the observed drop in ferritin and the rise in serum iron and transferrin saturation.[21,22]

A marked reduction in the ratios of patients with iron deficiency and IDA post-infection was noted. While we could not find any studies in the literature reporting the frequency of IDA before and after infection, several studies have shown that during infection, elevated hepcidin levels are positively correlated with ferritin levels and negatively correlated with serum iron levels.[23-25] This findings indicates that inflammation-induced iron sequestration might temporarily raise IDA rates during infection, with the true incidence of IDA becoming clear after the infection resolves.[18] This points to the importance of differentiating AI from true IDA, particularly in pediatric patients, as misdiagnosis could lead to inappropriate treatment strategies. One of the challenges in clinical practice is distinguishing between AI, commonly associated with infections, and true IDA. The mechanisms described above cause changes in iron metabolism during acute inflammation.[18-20] This results in a temporary, infection-related anemia that mimics IDA. Once the infection resolves, ferritin levels normalize and iron is released back into circulation, which may cause the previously exaggerated frequency of IDA due to the inflammatory response to return to its true values. Given this, clinicians must be cautious in diagnosing IDA during active infection. Serum ferritin, a marker for iron storage, can be misleading as it is elevated during inflammation. Instead, combining serum iron, transferrin saturation, and other markers like soluble transferrin receptor (sTfR) can provide a clearer picture of iron status.[26,27] In order to prevent misdiagnosis, it may be essential to reassess iron indicators once the infection has resolved.

The increase in hemoglobin, hematocrit, and erythrocytes in groups with and without IDA following infection suggests a recovery in erythropoiesis. After infection resolves, the release of iron from stores supports enhanced erythropoiesis, particularly in the bone marrow.[28] The increase in iron indicators in both groups is indicative of improved iron availability after the infection resolves. Among these indicators, only TIBC levels exhibited a more pronounced rise in the IDA group post-infection. As the inflammation resolves and iron becomes available again, the body increases TIBC to facilitate iron transport. Unlike in patients without IDA, where iron stores are relatively intact, IDA patients may rely more on circulating iron for erythropoiesis, leading to increased TIBC levels post-infection. On the other hand, studies have shown that transferrin, reflected by elevated TIBC, plays an immunoregulatory role by scavenging free iron and preventing it from facilitating the production of reactive oxygen species, thus influencing the inflammatory response.[29-31] Elevated CRP and leukocyte levels typically correlate with high hepcidin levels during infection, which leads to iron sequestration.[32] The more pronounced reduction in hepcidin levels after infection in IDA patients may have contributed to the greater decrease in inflammatory parameters and the more substantial rise in TIBC. These findings are in line with the possible role of hepcidin in the inflammatory response.[20,33]

Limitations

This study, despite providing useful insights into iron metabolism post-infection, is limited by its small sample size, which reduces the statistical strength and generalizability of the findings. Conducted at a single center, the results may not apply to broader populations, particularly given variations in healthcare and nutrition across regions. The study's reliance on only CRP and leukocyte levels as inflammatory markers, without considering key regulators like hepcidin or IL-6, limits the understanding of the mechanisms at play. Additionally, the lack of long-term follow-up restricts conclusions about recovery, and potential confounders such as diet or socioeconomic status were not accounted for. Finally, the type of infection was not stratified, though different pathogens may influence iron regulation in distinct ways.

CONCLUSION

This study underscores the complex interplay between iron metabolism and inflammation in pediatric infections, with notable shifts in iron parameters post-recovery. A significant reduction in both iron deficiency and IDA was observed after the infection, highlighting the body's capacity to restore iron balance once inflammation subsides. The marked improvements in hemoglobin, serum iron, and transferrin saturation, especially in IDA patients, emphasize the importance of addressing iron deficiency during recovery. These findings suggest that monitoring and managing iron levels post-infection is crucial to optimize recovery and prevent long-term iron depletion in children prone to infections.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was produced in the thesis study conducted in 2006.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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