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THE IMPACT OF IRON DEFICIENCY ANEMIA ON CYTOKINE PROFILES AND RESPIRATORY INFECTIONS IN CHILDREN: A SINGLE-CENTER STUDY

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Ключові слова: *залізодефіцитна анемія, цитокінові профілі, терапія препаратами заліза, респіраторні інфекції, харчовий статус*

Abstract. The impact of iron deficiency anemia on cytokine profiles and respiratory infections in children: a single-center study. Najafova V.A., Mammadova R.Y., Garayeva S.Z. *Iron deficiency anemia (IDA) is a common nutritional disorder in young children, associated with impaired cognitive, physical, and immune development. This study aimed to evaluate hematological, immunological, and nutritional parameters in children with IDA, determine the incidence of respiratory tract infections in IDA and assess the impact of iron supplementation therapy (IST). A prospective observational cohort study was conducted on 123 children aged 6 months to 5 years (95 term children with IDA and control group included 28 practically healthy children) between 2019-2020 at the National Center for Hematology and Transfusion in Baku, Azerbaijan. Laboratory assessments included hematological parameters, iron status markers, and immune system analysis using flow cytometry and ELISA. Hemoglobin (HgB), red blood cell (RBC) count, mean corpuscular volume (MCV), and ferritin levels were significantly lower in children with IDA compared to the control group ($p<0.001$), while total iron binding capacity (TIBC) and unsaturated iron binding capacity (UIBC) were elevated. Nutritional analysis revealed a significant deficiency in iron-rich food intake among children with IDA ($p<0.050$), with low socio-economic status and maternal education identified as key risk factors ($p<0.001$). Immune system evaluation showed significantly lower interferon gamma (IFN-γ) and interleukin-2 (IL-2) levels ($p<0.001$) and higher tumor necrosis factor alpha (TNF-α) levels ($p=0.003$), indicating compromised cellular immunity. The incidence of acute respiratory viral infections and pneumonia was significantly higher in children with IDA ($p<0.050$). IST over 8-16 weeks led to significant improvements in hematological and immune parameters, with a notable reduction in infection rates ($p<0.001$). It was proven the negative impact of IDA on immune function and its association with increased susceptibility to infections. IST effectively restores immune function and reduces infection incidence, emphasizing the importance of early diagnosis and intervention in pediatric IDA management.*

Реферат. Вплив залізодефіцитної анемії на цитокінові профілі та респіраторні інфекції в дітей: одноцентрове дослідження. Наджафова В.А., Мамедова Р.Й., Гараєва С.З. *Залізодефіцитна анемія є поширеним порушенням харчування в дітей раннього віку, що асоціюється з порушенням когнітивного, фізичного та імунного розвитку. Це дослідження було спрямоване на оцінювання гематологічних, імунологічних та нутритивних показників у дітей із залізодефіцитною анемією та оцінювання впливу терапії препаратами заліза. Проспективне обсерваційне когортне дослідження було проведено серед 123 дітей віком від 6 місяців до 5 років (95 доношених дітей із залізодефіцитною анемією та контрольна група з 28 практично здорових дітей) у 2019-2020 роках у Національному центрі гематології та трансфузіології в м. Баку, Азербайджан. Лабораторні дослідження включали гематологічні показники, маркери статусу заліза та аналіз імунної системи за допомогою проточної цитометрії та ІФА. Рівні гемоглобіну, кількість еритроцитів, середній об'єм еритроцита та рівень феритину були достовірно нижчими в дітей із залізодефіцитною анемією порівняно з контрольною групою ($p<0,001$), тоді як загальна залізозв'язувальна здатність сироватки та ненасичена залізозв'язувальна здатність*

були підвищеними. Аналіз харчування виявив значний дефіцит споживання продуктів, багатих на залізо, серед дітей із залізодефіцитною анемією (p<0,050), причому низький соціально-економічний статус та освіта матері були визначені як ключові фактори ризику (p<0,001). Оцінка імунної системи показала достовірно нижчі рівні інтерферону гамма та інтерлейкіну-2 (p<0,001), а також вищі рівні фактора некрозу пухлин альфа (p=0,003), що свідчить про порушення клітинного імунітету. Частота гострих респіраторних вірусних інфекцій та пневмонії була достовірно вищою в дітей із залізодефіцитною анемією (p<0,050). Проведення терапії препаратами заліза протягом 8-16 тижнів привело до значного покращення гематологічних та імунологічних показників, а також до помітного зниження частоти інфекцій (p<0,001). Доведено негативний вплив залізодефіцитної анемії на функцію імунної системи та її зв'язок зі зростанням сприйнятливості до інфекцій. Терапія препаратами заліза ефективно відновлює імунну функцію та знижує частоту інфекцій, що підкреслює важливість ранньої діагностики та втручання в лікуванні залізодефіцитної анемії в дітей.

Iron deficiency anemia is a problem of serious public health significance that impacts mental and physical development, health maintenance, and work performance [1]. World Health Organization (WHO) estimates that about to two billion people or 25% of the world's population are anemic, and approximately half of them suffer from IDA [2].

Anemia was found to be significantly associated with acute lower respiratory tract infections in children under five years of age. Prevention of anemia, irrespective of etiology, early diagnosis and treatment is important to reduce the incidence of lower respiratory tract infections in children [3]. Proliferation and effector functions of T cells are energy expensive processes that require iron for many metabolic and redox reactions involved as well as heme and Fe-S-containing enzymes that are indispensable for cell division and cytokine production [4].

Aim of the work – to determine the effect of iron deficiency anemia on cytokine fractions in children with high iron requirements during periods of intensive growth, to investigate the relationship between iron metabolism parameters and immunological markers, to assess nutritional parameters, and to assess the role of IDA and iron supplements in the incidence of respiratory tract infections.

MATERIALS AND METHODS OF RESEARCH

This prospecitve case-control study was conducted at the National Center for Hematology and Transfusion in Baku, Azerbaijan, from September 2019 to December 2020. The study included 123 children aged 6 months – 5 years. Clinical and anthropometric evaluations were conducted at the Pediatric Polyclinic Department. As part of secondary data collection, the mothers completed a structured questionnaire that included questions on nutrition, socioeconomic status, and medical history.

Ethical approval was granted by the Ethics Committee of the Azerbaijan State Institute for Advanced Medical Training named after A. Aliyev (Protocol No. 4, dated May 14, 2019). Written informed consent was obtained from parents or legal guardians of all participants.

Study Groups. IDA group: 95 term children diagnosed with iron deficiency anemia who had not received iron supplementation in the previous 12 months (58 boys, 37 girls). Children with concomitant inflammatory, parasitic, or genetic diseases were excluded. Control group: 28 apparently healthy children undergoing routine medical check-ups, with normal hematological parameters and no history of anemia, infections, or other pathological conditions based on clinical examination results (16 boys, 12 girls).

The distribution of the age variable was tested using the Shapiro-Wilk test. Normality was observed in both the control and main groups (W=0.96, p=0.38 and W=0.91, p=0.42, respectively). A parametric test was used to compare the age variable between the groups. There were no significant differences in age between groups (IDA: 23.0 [12; 49] months; Control: 21.5 [10.3; 40.5] months; p=0.891, Student's t-test).

Stratification and Exclusion Criteria. The IDA group was stratified by anemia severity: mild: 32 children 23.0 [12.5; 44.8] months 33.7%, moderate: 37 children 23.0 [12.0; 48.0] months 39.0%, severe: 26 children 23.0 [13.3;53.3] months 27.4%.

Exclusion criteria included preterm birth (gestational age <36 weeks), anemia due to chronic inflammatory diseases, acute inflammatory diseases, parasitic infestations, hereditary and genetic disorders, vitamin B12 and folic acid deficiencies.

All laboratory assessments were performed at the Clinical Diagnostic Laboratory of the National Center and the Central Scientific Research Laboratory of Azerbaijan Medical University. Hematologic and biochemical parameters were measured using standard methods. Complete blood count was performed using the Sysmex XN-1000 digital analyzer and Fluorocell WDF reagent (Sysmex Corporation, Japan) by the cytometry (cytofluorometry) method [5].

– For the assessment of iron status biochemical indicators (serum iron, total iron-binding capacity, unsaturated iron-binding capacity, transferrin saturation index), the Chromazurol B (CAB) method [6] was applied using the fully automated Biolis 30i analyzer (Ethernet LAN, Japan) and Human reagents (Germany).

– For the determination of total protein and C-reactive protein indicators, the Biuret method [7] was used with the fully automated Biolis 30i analyzer (Ethernet LAN, Japan) and Human reagents (Germany). Serum levels of interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) were quantified using enzyme-linked immunosorbent assay (ELISA) kits [8], according to manufacturer protocols. Sensitivity and reference ranges were provided by the manufacturers.

Follow-up Subset: In a subgroup of 35 children from the IDA group who completed 8-16 weeks of oral iron therapy, follow-up testing was conducted. Post-treatment assessments included hematological indices, iron status, and cytokine levels.

Statistical Analysis: Statistical analysis was performed using Microsoft Excel 2016 and IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). The analyses were conducted under a licensed academic subscription. Descriptive statistics were calculated for all variables, including median [Q1; Q3]. Statistical methods, including the choice of non-parametric tests, were selected and applied based on standard biostatistical principles [9].

Comparisons between groups were conducted using non-parametric tests, such as the Mann-Whitney U test, Wilcoxon signed-rank test, and Kruskal–Wallis H test, as appropriate. Categorical variables were assessed using Pearson's chi-square test (χ^2) and Fisher's exact test (two-sided). Receiver Operating Characteristic (ROC) curve analysis was used to assess the diagnostic performance of cytokine markers. The area under the ROC curve (AUC) was calculated to evaluate sensitivity and specificity. Student's t-test was used to compare means of normally distributed variables between groups. The Spearman correlation coefficient (ρ) was applied to examine the relationship between quantitative variables. Additionally, binary logistic regression analysis was used to identify independent predictors of iron deficiency anemia. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength and precision of associations between socio-demographic factors (e.g., maternal education level, household income) and the likelihood of IDA. A p-value of <0.05 was considered statistically significant throughout the study.

RESULTS AND DISCUSSION

A statistically significant decrease was observed in HgB concentration, RBC count, mean corpuscular hemoglobin (MCH), MCV, and hematocrit (HCT) levels in the study group compared to the control group. Specifically, HgB concentration in the study group was 85.00 [69; 92] g/L, whereas in the control group, it was 117.0 [116; 120] g/L ($p_u<0.001$). The RBC count was 3.4 [3.2; 3.5]$\times10^{12}$/L in the study group and 4.2 [4.1;4.4]$\times10^{12}$/L in the control group ($p_u<0.001$).

MCH values were 23.9 [22.2; 25] pg in the study group and 28.3 [27.9; 28.8] pg in the control group ($p_u<0.001$). Similarly, MCV values were 71.7 [68.6; 73.4] fL in the study group and 81.5 [80.2; 82.2] fL in the control group ($p_u<0.001$). HCT levels were 24.0 [22.0; 25.6]% in the study group, compared to 34.5 [34.0; 35.5]% in the control group ($p_u<0.001$). The erythrocyte sedimentation rate (ESR) was significantly elevated in the study group 13.0 [11;15] mm/h, compared to the control group 8.0 [8.0; 10.0] mm/h ($p_u<0.001$).

Total protein levels were also significantly lower in the study group 62.8 [61.2; 63.4] g/L than in the control group 66.0 [65; 67] g/L, ($p_u<0.001$). This reduction may be attributed to insufficient dietary intake of protein-rich foods, particularly meat pro ducts, among children in the study group. However, no statistically significant difference was observed in C-reactive protein levels between the study and control groups ($p_u=0.108$).

The hematological parameters depending on the severity of iron deficiency anemia in children are presented in the Table below.

Iron Status Indicators: Serum iron levels were significantly lower in the study group 7.9 [7.2; 8.3] μmol/L compared to the control group 14.1 [11.1; 18.0] μmol/L ($p_u<0.001$). Transferrin saturation was also markedly reduced in the study group 9.9 [9.0; 10.8]%, compared to the control group 25.0 [24.1; 26.7]% ($p_u<0.001$). Serum ferritin levels were significantly lower in the study group 8.4 [7.1; 9.7] ng/mL than in the control group 54.4 [44.8; 63.9] ng/mL ($p_u<0.001$). TIBC and UIBC were significantly elevated in the study group, with TIBC at 78.3 [76; 81.1] μmol/L and UIBC at 71.1 [67.9; 73.5] μmol/L. In contrast, TIBC and UIBC levels in the control group were 56.9 [53.7; 58.8] μmol/L and 42.2 [40.3; 43.6] μmol/L, respectively ($p_u<0.001$). These findings provide strong evidence supporting the diagnosis of IDA in the study group, highlighting significant alterations in hematological and iron status parameters.

A significant deficiency of iron-rich foods was observed in the dietary intake of children aged 6 months to 5 years diagnosed with IDA in the study group ($p_{\chi^2}<0.050$; $p_F<0.050$). Additionally, the socio-economic status of families in both study and control groups was analyzed as a potential risk factor for IDA development (Fig. 1).

Table 1

Evaluation of Hematological Parameters Depending on the Severity of Iron Deficiency Anemia in Children (Median [Q1; Q3])

Parameters	Mild Degree (n=32)	Moderate Degree (n=37)	Severe Degree (n=26)	p_{u_1}	p_{u_2}	p_H
Hb, g/L	94.0[92,0;98,0]	85.0[79,0;85,0]	66.0 [63.8;66,0]	<0.001	<0.001	<0.001
RBC $\times 10^{12}$/L	3.5 [3.4;3.6]	3.4 [3.2; 3.4]	3.2[2.9; 3.2]	0.006	0.044	<0.001
Hematocrit, %	25.0[25.3;26.4]	23.8 [23.3;23.8]	21.0 [20.1;21,0]	0.047	0.029	<0.001
MCH, pg	25.0[24.6;26.0]	24.1[23.2; 24.1]	20.6[19.8;20.6]	<0.001	<0.001	<0.001
MCV, fL	73.0 [72.5;74.4]	71.7[70.3; 71.7]	66,4 [63.9; 66.4]	<0.001	<0.001	<0.001
MCHC, g/dL	27.0 [26.7; 28.0]	26.7[26.2; 26.7]	24,9 [19.6;24.9]	<0.001	<0.001	<0.001
ESR, mm/hr	11.0 [10; 12.8]	12.0[11,0;12,0]	15.0[14,0;15.5]	<0.001	<0.001	<0.001

Notes: statistical significance p<0.050 (based on Mann-Whitney U test); p_{u1} - between mild and moderate IDA groups; p_{u2} - between moderate and severe IDA groups; p_H - significance level of Kruskal-Wallis H-test among groups.

According to the findings, the proportion of mothers with complete or incomplete secondary education was 70.5% in the study group and 35.7% in the control group. A statistically significant difference was identified between the two groups (χ^2=11.194, p_{χ^2}<0.001; F=0.002, p_F<0.050). Economic status analysis revealed that 76.8% of children in the study group belonged to low-income families, compared to 28.6% in the control group. This difference was statistically significant (χ^2=22.409, p_{χ^2}<0.001; F<0.001, p_F<0.050).

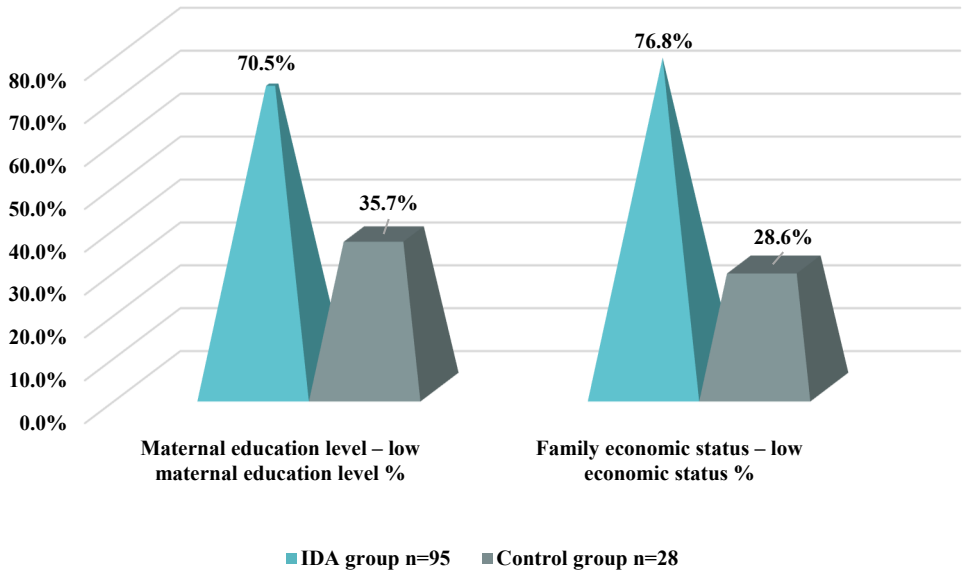

Fig. 1. Assessment of socio-economic status of families with IDA children and control group

Since iron deficiency leads to an inadequate immune response, key cytokine fractions (IL-2, INF-γ, TNF-α), which serve as major immune indicators, were analyzed during the study. A binary logistic regression model was developed to analyze maternal education level and family socio-economic status as risk factors for the development of IDA (Table 2). The binary logistic regression analysis indicated that low maternal education level (OR=3.857, 95% CI [1.615–9.213]; p=0.002) and low socio-economic status (OR=7.273, 95% CI [2.898–18.254]; p<0.001) significantly contribute to the occurrence of IDA.

Table 2

Regression coefficients and odds ratios (with 95% CI) for risk factors in children with IDA

Parameters		p value	Odds ratio (95% CI)
Maternal education level	**low maternal education level**	**0,002**	**3,857 (1,615-9,213)**
Family socio-economic status	**low socio-economic status**	**<0,001**	**7,273 (2,898-18,254**

Notes: logistic regression analysis was performed to assess independent risk factors for IDA. OR – odds ratio; CI – confidence interval. Statistical significance was set at p<0.05.

The analysis of selected cytokine fractions (INF-γ, TNF-α, IL-2) in children from the study group is presented in Figure 2.

In the study group, the IFN-γ level was 1.7 [1.0; 2.2] pg/mL while in the control group, it was 3.0 [2.9;3.2] pg/mL. A positive correlation was observed between IFN-γ and HgB, serum iron, and serum ferritin with correlation coefficients of ρ=0.890, p<0.001; ρ=0.682, p<0.001; and ρ=0.604, p<0.001, respectively. The TNF-α levels were also analyzed in the study groups. In the study group, TNF-α was 3.1 [2.7; 4.1] pg/mL, whereas in the control group, it was 1.9 [1.4; 2.1] pg/mL. A 1.9-fold statistically significant increase was observed in the study group compared to the control group (p_u=0.003). TNF-α exhibited a weak negative correlation with HgB, serum iron, and serum ferritin (ρ= -0.454, p=0.001; ρ= -0.323, p=0.001; ρ= -0.310, p=0.002, respectively). Given that TNF-α is a pro-inflammatory cytokine, its elevated levels may be associated with inflammatory processes occurring in IDA.

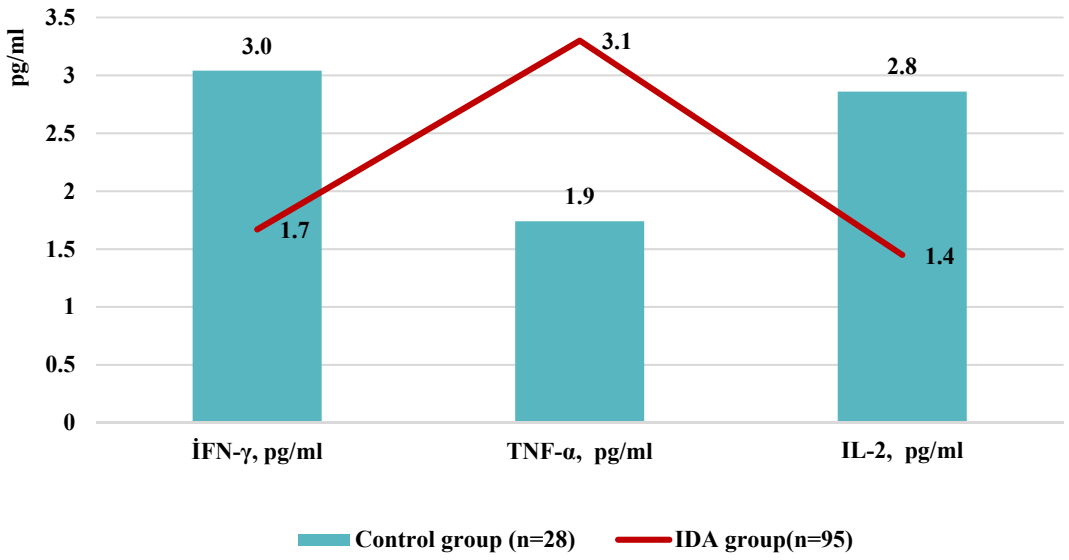

Fig. 2. Comparative analysis of cytokine fractions between the IDA and control group

IL-2 is a critical cytokine for T cell peripheral tolerance and immunity [10], its levels were also assessed during the study. The IL-2 level in the study group was 1.4 [0.8; 1.9] pg/mL, while in the control group, it was 2.8 [2.7; 3.0] pg/mL. The IL-2 level in the study group showed a 2.0-fold statistically significant decrease compared to the control group (p_u<0.001). Additionally, IL-2 demonstrated a positive correlation with HgB, serum iron, and serum ferritin, with correlation coefficients of ρ=0.810, p<0.001; ρ=0.712, p<0.001; and ρ=0.711, p<0.001, respectively. Since IFN-γ and IL-2 are key cytokines involved in cellular immune responses, their reduced levels in the study group suggest a potential weakening of cell-mediated immunity in IDA.

Given the observed immune imbalance, the incidence of upper and lower respiratory tract infections among children with IDA was examined (Table 3). As shown in Table 2, the annual frequency of acute respiratory viral infections (ARVI) (more than four times

per year) was 61.1% (58 children) in the study group, compared to 17.9% (5 children) in the control group.

In the study group, the incidence of pneumonia was 17.9% (17 children), whereas no cases were recorded in the control group. A statistically significant difference was observed between the study and control groups (χ^2 =5.814, p_{χ^2} =0.016, F=0.012, p_F<0.050).

Table 3

Comparison of respiratory infection incidence between the IDA and control group

Parameters	Control group (n=28)		IDA group (n=95)		p_{χ^2}	p_F
	absol.numb	%	absol.numb	%		
ARVI (more than 4 times per year	5	17.9	58	61.1	<0.001	<0.050
Pneumonia	0	0	17	17.9	0.016	<0.050

Notes: χ^2 – Pearson's chi-square test; F – Fisher's exact test. Statistical significance was considered at p<0.05.

Based on the ROC curve analysis, the area under the curve (AUC) for IFN-γ was 0.974±0.015 pg/mL (95% CI: 0.944–1.003, p<0.001), for TNF-α, it was 0.083±0.026 pg/mL (95% CI: 0.033–0.133, p<0.001), and for IL-2, it was 0.964±0.016 pg/mL (95% CI: 0.932–0.996, p<0.001) (Fig. 3, Table 4).

The cutoff values for INF-γ, TNF-α, and IL-2 in children with IDA were determined as <2.35 pg/mL, >3.25 pg/mL, and <1.85 pg/mL, respectively. The sensitivity and specificity for INF-γ, TNF-α, and IL-2 were 82.1%, 42.1%, and 71.6% for sensitivity, and 100.0%, 100.0%, and 100.0% for specificity, respectively.

During the study, iron metabolism parameters (hematological and iron status indicators) were comparatively analyzed in 35 children aged 6 months to 5 years with iron deficiency anemia before and after replacement therapy with iron-containing preparations (iron (II) sulfate, iron(II) gluconate, iron (III) hydroxide polymaltose). Iron-containing preparations (in the form of syrup and drops) were administered orally at a dose of 3-6 mg/kg (elemental iron) for 8-16 weeks, taking into account the severity of the IDA, the age and weight of the children. Treatment in children with mild, moderate, severe IDA was carried out on an outpatient basis.

Our research examined changes in cytokine fractions (INF-γ, TNF-α, IL-2) before and after replacement therapy with iron supplements in 35 children with IDA (Fig. 4). Prior to treatment, IFN-γ levels in the IDA group were 1.6 [1,0; 2,0] pg/ml, whereas in the control group, they were 3.0 [2.9;3.2] pg/ml (p_u<0.001). TNF-α levels were 3.1 [2.4; 4.2] pg/ml and 1.9 [1.4; 2.1] pg/ml, respectively (p_u<0.001), while IL-2 levels were 1.4 [0.6; 1.8] pg/ml in the IDA group and 2.8 [2.7; 3.0] pg/mL in the control group (p_u<0.001). The reduced levels of IFN-γ and IL-2 suggest a weakened cellular immune response in children with IDA.

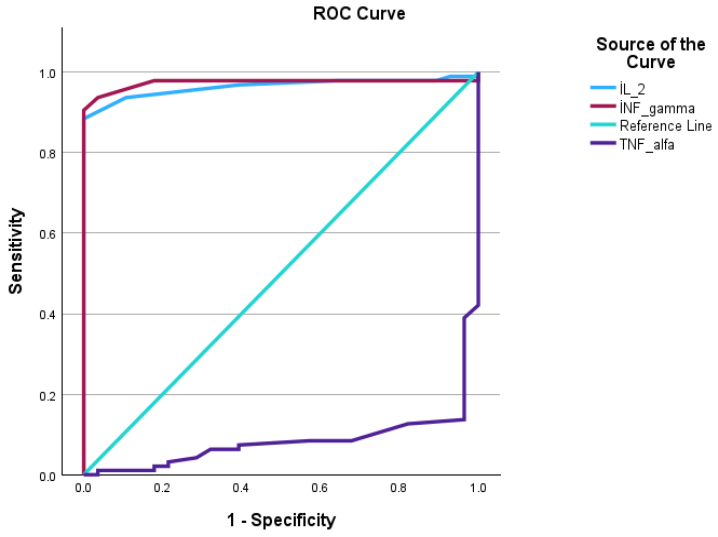

Fig. 3. ROC curve of IFN-γ, TNF-α and IL-2 markers in children with IDA

Table 4

AUC-ROC analysis of IFN-γ, TNF-α, and IL-2 markers in children with IDA

Parameters	Area	Standard error	Stat. sig. (p)	95% Confidence Interval	
				lower bound	upper bound
IFN- γ	0.974	0.015	<0.001	0.944	1.003
TNF-α	0.083	0.026	<0.001	0.033	0.133
IL-2	0.983	0.016	<0.001	0.932	0.996

Notes: ROC – Receiver Operating Characteristic; AUC – Area Under Curve. Statistical significance was set at $p<0.05$.

After replacement therapy, IFN-γ levels increased significantly from 1.6 [1,0; 2,0] pg/ml to 3.9 [3.5; 4.4] pg/ml ($p_w<0.001$), approaching the levels observed in the control group. This positive dynamic of IFN-γ can be considered an indicator of effective treatment. TNF-α levels decreased from 3.1 [2.4; 4.] pg/ml to 1.8 [1.4; 2.1] pg/ml after therapy, with a reduction observed in 32 out of 35 children, while no change was noted in 3 children ($p_w<0.001$). Since TNF-α is a pro-inflammatory cytokine, its decline may be associated with a reduction in inflammatory processes occurring in IDA. The decrease in TNF-α levels post-treatment suggests a beneficial therapeutic effect.

IL-2 levels increased significantly from 1.4 [0.6; 1.8] pg/ml before treatment to 3.5 [2.9; 3.9] pg/ml after treatment. This rise was statistically significant across all children in the IDA group ($p_w<0.001$), further supporting the immunomodulatory effects of iron therapy.

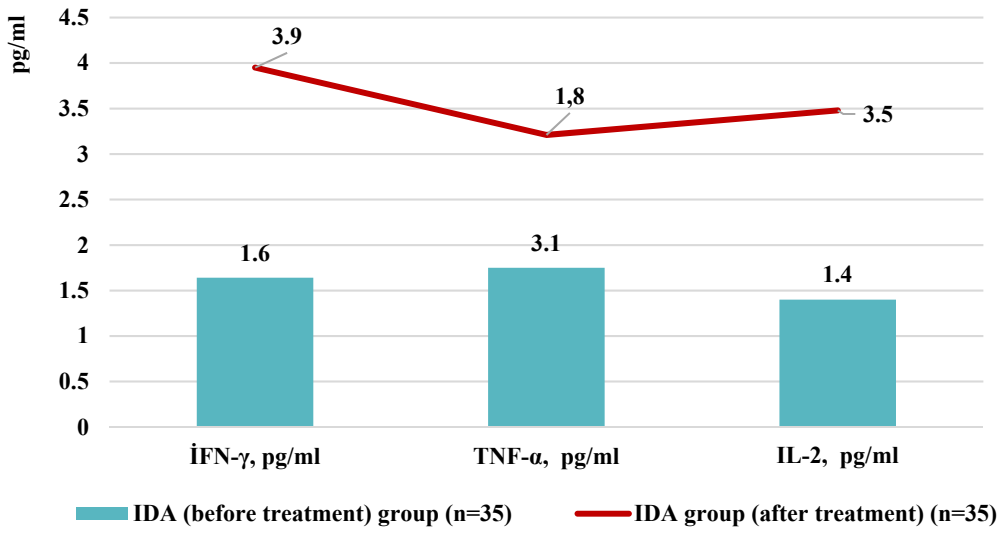

Fig. 4. Results of cytokine fractions in the treatment dynamics of the IDA group

The frequency of upper and lower respiratory tract infections was assessed in the IDA group before and after treatment (Fig. 5).

The annual incidence rate of ARVI (more than four times per year) was observed in 17 children (48.6%) before treatment and in 2 children (5.7%) after treatment. A statistically significant difference was recorded between the groups ($\chi^2=16.254$, $p_{\chi 2}<0.001$, $F<0.001$, $p_F<0.050$).

The frequency of lower respiratory tract infections (pneumonia) was observed in 8 children (22.3%) in the pre-treatment IDA group, while no cases were recorded in the post-treatment group. A statistically significant difference was also noted between the groups ($\chi 2=9.032$, $p_{\chi 2}=0.003$, $F=0.002$, $p_F<0.050$).

In the treatment dynamics of the IDA group, the levels of IFN-γ and IL-2 significantly increased after treatment compared to the pre-treatment period by 2.4 and 2.5 times, respectively ($p_w<0.001$). The level of TNF-α decreased significantly by 1.8 times after treatment compared to the pre-treatment period ($p_w<0.001$).

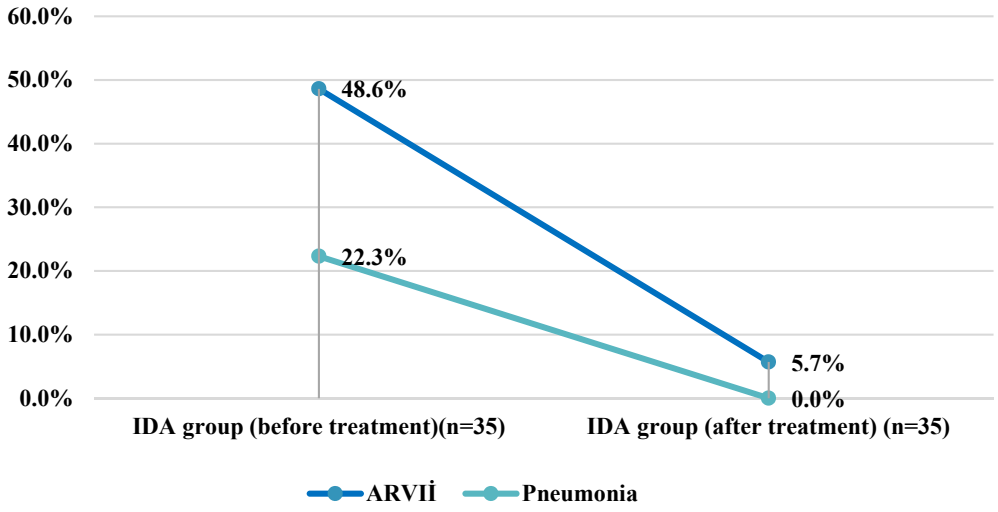

Fig. 5. Comparative analysis of the frequency of upper and lower respiratory tract infection before and after treatment in the IDA group

Thus, the positive dynamics of INF-γ, TNF-α, and IL-2 after treatment, along with a statistically significant reduction in children's complaints and respiratory tract infections, can be considered an effective outcome of the treatment.

There is a close interconnection between iron metabolism and immunity. This is largely due to the production of cytokines from immune cells including T cells and macrophages under certain physiological conditions. These cytokines regulate the iron-handling proteins involved in the uptake, storage and release of iron [11]. IL-2 plays an important role as a growth factor that induces the proliferation of CD8+ and CD4+ T cells. It also has many other biological roles including the induction of the proliferation of Natural Killer cells (NK), the increment of cytolytic activity, the promotion of antibody production and B cell proliferation [12]. Researchers have demonstrated a significant positive correlation between IL-2 gene expression and red blood cell count, mean corpuscular hemoglobin concentration, serum ferritin level, serum iron level, T lymphocyte cells count ($CD3^+$), cytotoxic T lymphocyte cells count ($CD3^+$ $CD8^+$), and mean fluorescence intensity of $CD3^+$ $CD8^+$ cells [13]. IL-2 is a major modulator of the development, homeostasis and functions of various T cell subsets, and therefore has key role in orchestrating the balance of adaptive immune responsiveness [14].

Type II IFN (IFN-II), also known as gamma interferon (IFN-γ) is mainly produced by activated T cells, natural killer (NK) cells, and some other immune cells. It stimulates the production of antibodies and enhances antigen presentation to T cells playing a crucial role in the adaptive immune response, particularly in Th1 cell differentiation [15]. Certain IFNG gene polymorphisms (e.g. IFNG+2200C) were associated with lower hemoglobin and a trend toward iron deficiency anemia, though statistical significance was limited. It shows potential genetic influence of IFN-γ on anemia risk [16].

T-cell activation is regulated through IL-2-dependent pathways, including iron uptake via the transferrin receptor (CD71) [17]. IFN-γ regulates the synthesis of iron-related proteins such as hepcidin, ferroportin, and ferritin and stimulates iron export from macrophages [18].

Thus, it is important to emphasize that iron deficiency is a common clinical condition frequently encountered in medical practice. Beyond its role in erythropoiesis, iron plays a crucial role in immune defense mechanisms. Iron deficiency can affect cytokine activity through various pathways, potentially increasing susceptibility to infections.

CONCLUSION

1. The levels of interferon-gamma and interleukin-2 in the main group were 1.4 times and 2.0 times statistically significantly lower than in the control group, respectively (p_u<0.050). According to the ROC curve, the cut-off points for interferon-gamma and interleukin-2 indicators were found to be 2.35 pg/ml and 1.85 pg/ml, the sensitivity – 82,1% and 71,6%, and the specificity – 100.0% and 100.0%, respectively.
2. After taking iron supplements for 8-16 weeks, cellular immunity indicators (interferon-gamma, interleukin-2) in the main group showed a statistically significant increase (p_w<0.050) compared to the pre-treatment period and approached the levels of the control group.

3. The high incidence of respiratory tract infections in children with iron deficiency anemia is associated with a deficiency in cellular immunity. Among children in the main and control groups, acute respiratory viral infections (more than 4 times a year) were observed in 61.1% and 17.9%, respectively ($p_{\chi 2}$<0,001; p_F<0,050), pneumonia was not observed in the control group, while in the total iron deficiency anemia group, it was 17.9% ($p_{\chi 2}$=0,016; p_F<0,050). The decrease in the incidence of respiratory tract diseases after treatment with iron preparations (p_F<0.050) is attributed to the positive effect of treatment on the activity of immune indicators.

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Najafova V.A. – investigation, data curation, formal analysis, software, writing – original draft;

Mammadova R.Y. – project administration, investigation, data curation;

Garayeva S.Z. – conceptualization, validation, resources, funding acquisition, – writing – review & editing, visualization;

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