HEALTH, ENVIRONMENT, DEVELOPMENT

EXPENDITURE OF IRON DEFICIENCY SCREENING IN ADOLESCENTS BY DETERMINATION OF BLOOD FERRITIN

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Summary

The aim: Substantiation of the expediency of screening for iron deficiency in adolescents of Ukraine, determining the relationship between blood ferritin levels and erythrocyte indices. Materials and methods: The literature data analizys and laboratory examinations of 699 patients in medical records throughout Ukraine in children aged 10-19 who applied for medical care in 2018. Results: According to the obtained data we found that there is no significant difference between the ferritin level ($p = 0.728$) between groups of urban and rural territory of inhabitance ($p = 0.728$)/ Total amount of children aged 10-15 years with ferritin below normal 7 ng / ml was 16.3%, of which men 7.7%, women 92.3%. According to European guidelines for the determination of iron deficiency, the number of children with ferritin levels less than 30 ng / ml in this group is 63%, of which men 15.9% and women 84.1%. in a group aged 16 (297 results) the number of male children with ferritin levels less than 22 ng / ml is 12%, and female children with ferritin levels less than 10 ng / ml – 31%. According to WHO recommendations with a rate of 30 ng / ml, the number of people with lower rates was 24% males 69% females. Conclusion: When using the reference values recommended by the WHO for the European region as a criterion for iron deficiency, the percentage of adolescents with iron deficiency increases mainly by 2 times in both the male and female groups.

Keywords: iron deficiency, adolescent, ferritin, screening, anemia.

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1. Introduction

Modern evidence-based medicine is aimed to prevent and to provide early diagnostic of diseases and conditions that can affect the overall health of the nation. Standardization systems and clinical routes are being developed to help to avoid inefficient and erroneous interventions,

unnecessary and unreasonable research, and material costs. The most effective measure to meet these needs is to conduct screening programs. Anemia is a clinical and hematological syndrome characterized by a decrease in the amount of iron in the serum, bone marrow and depot, which leads to a violation of the synthesis of hemoglobin and hence erythrocytes.

According to the WHO, anemia affects about 25% of the world's population, in Europe about 20% of the population, but this figure varies depending on the socio-economic conditions of the country. However, the vast majority of the total pool of anemias are iron deficiency, and megaloblastic (B12-deficient and folate-deficient), hemolytic, aplastic and anemia of chronic diseases.

There is an uneven distribution of anemia in the population age groups. Thus, the portion of preschool children with anemia is 47.4%; school-age children 25.4%; pregnant women 41.8%; non-pregnant women 30.2%; among men 12.7%; among the elderly 23.9%.

Anemic syndrome, which includes shortness of breath, rapid heartbeat, fatigue, dizziness, irritability – is often "masked" in children and adolescents by other pathologies, such as somatoform autonomic dysfunction, neuro-circulatory dystonia, chronic fatigue syndrome. For pregnant women, iron deficiency anemia is a threatening factor in pregnancy and childbirth, which can determinate an inadequate physical and mental development of the child.

According to WHO recommendations, iron deficiency screening is performed by detecting the level of ferritin. However, primary care physicians are equipped with hemanalyzers that do not allow to determine the biochemical parameters of the blood, but allow to determine the level of hemoglobin and physical qualities of erythrocytes.

2. The aim

Substantiation of the expediency of screening for iron deficiency in adolescents of Ukraine, determining the relationship between blood ferritin levels and erythrocyte indices.

3. Materials and methods

We studied the literature data according to the screening of iron deficiency anemia in adolescents in other countries, and analyzed subjective, clinical and laboratory examinations of 699 patients in medical records (which contained the ferritin levels) throughout Ukraine (except the military occupied regions) in children aged 10-19 who applied for medical care in 2018. Method used to detect ferrin – chemiluminescent immunoassay, measurement range: 0.5-82500.0, unit of measurement: nanograms per milliliter. The study was approved by the ethics commity NMAPE Shupik (protocol № 10, 05.11.2018).

4. Results

To perform the task of the study, we used the data of 699 medical histories with the results of ferritin analysis throughout Ukraine (except the military occupied regions) in children aged 10-19 who applied for medical care in 2018. Reference values of ferritin for children under 15 years of age in the laboratory is 7-140 ng / ml, for men over 15 years – 22-322 ng / ml, for women over 15 years of age 10-291 ng / ml. The study included data from 160 (23%) males and 539 (77%) females.

According to the obtained data we found that there is no significant difference between the ferritin level ($p = 0.728$) between groups of urban and rural territory of inhabitance ($p = 0.728$) (city group Me 21.2 (10.38; 40.4) and the village group Me 23.2 (9.65; 43.5)).

While comparing the groups by sex according to the Mann-Whitney test for independent samples with nonparametric distribution, a significant difference was found in the indicators of ferritin (p <0.001) between the group of females aged 10-19 years Me 17.9 (8.68; 32.85) and males Me 40.3 (22.75; 70.05).

Table 1

The distribution of ferritin data groups by age was as follows

Age	Number of partitipants	Withdrew from the study	Median	Q1	Q3
10	37		33	21,9	49,45
11	52	1	32,5	14,8	78,5
12	49		21,8	12,3	37,2
13	73		18,7	7,8	35,45
14	81		16,6	7,55	31,8
15	110	2	19,6	9,12	40
16	94	4	24,35	13,03	51,88
17	99		21,7	9,9	46,8
18	104	1	19,6	8,6	33,9

According to the comparison criterion H Kraskel-Wallis (with a posteriori analysis of Dunn) for three or more groups with nonparametric parameters, it was determined that ferritin data differ significantly between groups aged 10 and 14 years p = 0.002, between groups 11-14 years p = 0.003, between groups of 10 and 13 years p = 0,039 and between groups of 10 and 15 years p = 0,042. According to these results, the level of ferritin decreases significantly in children aged 13-15 years and continues to remain low until 18 years of age, as the differences between the groups of children aged 13-15 and 16-18 years. While checking correlations by Spearman's correlation analysis for continuous nonparametric data, it was determined that there is a direct significant correlation between ferritin and serum iron (N = 225, r^2 = 0,572; p <0,001), a significant inverse correlation between ferritin and transferrin. (N = 98, r^2 = – 0,693; p <0,001), direct moderate relationship between hemoglobin and ferritin (N = 230, r^2 = 0,471; p <0,001), weak insignificant relationship between erythrocyte count and ferritin level (N = 230, r^2 = 0,104; p = 0,116), a direct moderate correlation between the level of ferritin and the average erythrocyte volume (N = 227, r^2 = 0,333; p <0,001), and between ferritin and the average hemoglobin content in the erythrocyte (N = 227, r^2 = 0.333; p <0.001).

The part of children aged 10 to 15 years included in the study was 57% (399), of which men 27% (108), women 73% (291). 80% of children living in urban areas (319), 20% of children living in rural areas (80). The distribution was determined by the Kolmogorov-Smirnov criterion. The average values of ferritin for children from the city were Me 19.7 (10.1; 37.1), for children from the village – Me 27.35 (14.37; 44.2). According to the Mann-Whitney U test, a significant difference between the rural group and the urban group was found for independent samples with nonparametric distribution (p = 0.039).

Total amount of children aged 10-15 years with ferritin below normal 7 ng / ml was 16.3% (65), of which men 7.7% (5), women 92.3% (60). According to European guidelines for the determination of iron deficiency, the number of children with ferritin levels less than 30 ng / ml in this group is 63% (252), of which men 15.9% (40) and women 84.1% (212).

A comparative analysis of the Mann-Whitney U groups for independent samples with nonparametric distribution by sex in the age group of children under 15 years showed that there is a significant difference in ferritin levels between the group of male adolescents Me 35.7 (18.1; 57, 57) and adolescent females Me 17.9 (8.7; 32.55).

5. Discussion

All functions of erythrocytes are determined by their structure, so it is important to determine the shape and structure of erythrocytes. Erythrocyte indexes that can be suspected of iron deficiency anemia include mean erythrocyte volume (MCV) – an indicator expressed in fertoliters and when less than 80 fl is treated as microcytosis (reference values 80-100 fl); average hemoglobin concentration of erythrocytes (MCH) – an indicator that reflects the number of hemoglobin per erythrocyte in absolute numbers (reference values 27-35 pg), where iron deficiency anemia on this indicator is defined as a sign of hypochromia (central lumen of erythrocytes more than 1/3 – the diameter of the cell) MCH <27 pg. As microcytosis occurs in a variety of hereditary and acquired hemoglobinopathies, including a variety of erythrocytes depending on ethnic groups, thalassemia, feritin is determined as the further step to figure the diagnosis definitely out.

The referent values for ferritin in Ukraine depend on age and stand for: newborns – 25–200 ng / ml (95% confidence interval (CI) 25–200 μg / l); children aged 1 month – 200-600 ng / ml (95% CI 200-600 μg / l); 2–5 months – 50–200 ng / ml (95% CI 50–200 μg / l); 6 months – 15 years – 7–140 ng / ml (95% CI 7–140 μg / l); adult men – 20-300 ng / ml (95% CI 20-300 μg / l); adult women – 20–120 ng / ml (95% CI 20–120 μg / l). However, according to WHO recommendations, ferritin levels for the European population less than 20 ng / ml are considered to be an indicator of iron deficiency, which requires medication and dietary correction, taking to account this norm for children aged 10-19 years as well.

Literature data show that the hemoglobin level reacts late to the decrease in blood iron stores, and the typical symptoms of anemia begin to appear at a low hemoglobin level. Therefore, erythrocyte indices (hypochromia and microcitosis), hematocrit decrease, increase in the width of erythrocyte size distribution are more indicative. Factors influencing the result of the laboratory test include blood transfusion carried out very close before the study (possible increase).

However, there is still the leck of researches, that have been conducted according to the topic of development of iron deficiency without anemia in adolescents in developing countries and their iron status in adulthood. *(Jáuregui-Lobera, 2014:10, 2087)* Anemia affects a quarter of the world's population, holding 8.8% of the global disease burden. There is a tendency in the world to increase the prevalence of anemia with age-growth and for hospital treating patiants. Anemia reduces efficiency and increases health care costs. Iron deficiency without anemia is common among both sexes, but the proportion of women is undoubtedly dominant. The relationship between iron deficiency without anemia and restless legs syndrome (RLS), cognitive impairment, decreased quality of life, fatigue and infertility has been identified and corrected by supplementing with iron supplements. Various gastrointestinal conditions, such as celiac disease, inflammatory bowel disease, chronic kidney disease, increase the risk of iron deficiency anemia and clinically significant latent iron deficiency. *(Jimenez et al., 2015: 241)* Adolescents are defined as a "risk group" for eating disorders. They are prone to high food demand due to rapid growth and at the same time reducing the caloric content of the diet and malnutrition for nutrients due to the tendency to a marginal worldview. *(Jáuregui-Lobera, 2014:10, 2087)* Severe iron deficiency is often associated with anemia, but iron deficiency is also possible with

normal hemoglobin levels, which in turn affects quality of life, the comorbidity's condition, and the manifestation of mental disorders and their severity. The appearance of mental disorders in adolescents often indicates a hidden long-term illness and leads to the figuring the iron deficiency out as one of the important risk factors. *(Du Plessis et al., 2019: 1-6)*

The importance of iron in cognitive function is emphasized in some studies where changes in psychomotor development and cognitive function are usually associated with iodine and iron deficiency, which may be accompanied by long-term behavioral changes. In general, iron deficiency in the neonatal period and early childhood is considered a key risk factor for cognitive impairment. At the same time, the scientific and medical community still does not reach a common consensus on the effectiveness of possible prevention programs. Still additional study requires the effectiveness of screening diagnostic measures, the nutritional composition of the diet, the frequency and amount of food intake. *(Jáuregui-Lobera, 2014:10, 2087)*

Iron deficiency and iron deficiency anemia are associated with an increased risk and early onset of psychiatric illness, such as unipolar depression, bipolar disorder, chronic fatigue syndrome, autism spectrum disorder, attention deficit hyperactivity disorder, impaired neurodevelopmental development and severity.

Iron is crucial in the functional development of the brain. Iron deficiency can affect the bioavailability of dopamine, norepinephrine and serotonin in various areas of the brain and is associated with delayed psychomotor development in infants and cognitive impairment throughout childhood and adolescence. [3] This contributes to poor sleep quality, lethargy and potentially long-term sleep, causing behavioral changes.

In 2011-2012, the prevalence of dyslipidemia among children in developed countries reached 20.2%, taking into account that 1 in 5 adolescents faced an increased risk of atherosclerosis, which influences the percentage of this disease among the adult population. The hypothesis of dependence of iron metabolism in the development of oxidative stress and prosaic processes was proposed. Additionally, epidemiological studies have shown an association between serum iron and ferritin stores, blood lipid concentrations and oxidative stress in children and adults. A study was conducted in an urban area of China, which included 1,866 children aged 7-18 years who did not have genetic, endocrine and acute pathologies at the time of the survey. The results of the study showed that the parameters of iron metabolism were associated with body mass index and lipid profile in children and adolescents.

The study showed that serum iron levels decreased in proportion to BMI, while ferritin levels peaked in obese subjects, suggesting that iron storage was closely related to BMI in children and adolescents. On the other hand, children and adolescents with dyslipidemia had lower levels of iron, serum transferrin, and sTfR, and higher levels of ferritin in obese individuals. In addition, there have been significant inverse associations between transferrin and sTfR concentrations and the risk of dyslipidemia in children, which may be inversely related to the risk of atherosclerosis and related cardiovascular disease in adulthood. *(Zhu Y. et al., 2019 : 1-8)*

Some studies have suggested possible genetic abnormalities such as lysosomal storage diseases or mitochondrial lysosomal abnormalities that interfere with the transport of protein, calcium and iron. *(Linert et al., 2012)*

Small hypochromic erythrocytes are formed in iron-deficient conditions, but in general due to the alimentary insufficiency, which is often for the adolescent population, there may be co-occurrence of folic and B12-vitamin insufficiency, which heamatological are characterized by macrocytosis. In such cases, iron deficiency is observed without changes in the erythrocyte lineage, or the presence of normocytic hypochromic erythrocytes. To determine the status of iron in these cases, it is recommended to determine transferrin, iron-binding capacity of

erythrocytes, serum iron and ferritin. *(Jimenez et al., 2015:241)* To diagnose iron deficiency, the determinant levels of TfS are below 20% and the level of ferritin is below 30 ng / mL. As ferritin is known as an inflammatory protein, it is recommended to determine the C-reactive protein to avoid misinterpretation of the results.

It is known that external factors such as living above sea level and smoking increase the concentration of hemoglobin. Accordingly, there is a high probability of underestimating the prevalence of anemia among people living at high altitudes and among smokers if we apply the standard reference values of hemoglobin. In 2011, the WHO proposed amendments to define anemia depending on the landscape of the place of residence as well as the smoking status. Both amendments are recommended for smokers living high above sea level. There was also a difference in hemoglobin depending on ethnic groups, but so far there is insufficient evidence of the difference between them, so this error is not recommended to take into account in practice. *(World Health Organization, 2014)* Iron levels on the generalized norms do not suit for athletes who practice enhanced sport's activity. *(Jimenez et al., 2015:241)*

Blood sampling options – venous or capillary – also affect hemoglobin levels. Thus at definition of hemoglobin in capillary blood indicators can often be overestimated, in comparison with venous blood. *(World Health Organization, 2014)*

According to the Order of the Ministry of Health №709 of 02.11.2015, people who are highly likely to have iron deficiency anemia can be identified by certain risk factors. Paragraph 4.2 lists the primary factors which include the period of intensive growth of children, pregnancy up to 18 years of age, women with heavy menstrual losses. Much attention is also paid to conditions in which the absorption of iron decreases. Secondary reasons include low socio-economic status, donation, and vegetarianism. The need for primary diagnosis of celiac disease in the detection of microcytosis and hypochromia is especially emphasized. If there are risk factors, it is recommended to take a general blood test to check the level of hemoglobin, erythrocytes with erythrocyte indices, hematocrit, leukocytes with the formula and platelets. Only then, with changes in erythrocyte indices, it is recommended to determine ferritin to confirm the iron-deficient nature of anemia.

A total of 43% (300) of persons aged 16 and over dropped out of the study according to the exclusion criteria and 297 results were taken into account. The share of males among them was 50, females – 247. Among them, the number of male children with ferritin levels less than 22 ng / ml is 12% (6), and female children with ferritin levels less than 10 ng / ml – 31% (77). According to WHO recommendations with a rate of 30 ng / ml, the number of people with lower rates was 24% (12) males 69% (171) females.

The total number of men aged 16 and over 50. Among them, the number of people with ferritin levels less than 22 ng / ml is 6 people (12%). According to WHO recommendations *(World Health Organization, 2014)* with a rate of 30 ng / ml, the number of people with lower rates was 12 (24%). *(World Health Organization, 2011)*

The total number of women aged 16 and over is 247. Among them, the number of people with ferritin levels below 10 ng / ml is 77 people (31.2%). According to WHO recommendations with a rate of 30 ng / ml, the number of people with lower rates was 171 (69.2%).

6. Conclusions

1. There is the same situation regarding iron deficiency among adolescents aged 10-19 years in rural and urban areas in all territory of Ukraine.

2. Iron deficiency is common for females in Ukraine much more than males.

3. A significant decrease in ferritin levels among adolescents is observed from the age of 14 years and remains almost unchanged until 19 years.

4. When using the reference values recommended by the WHO for the European region as a criterion for iron deficiency, the percentage of adolescents with iron deficiency increases mainly by 2 times in both the male and female groups.

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Conflict of interests:
The authors declare no conflict of interest.