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FEATURES OF DIAGNOSIS AND CORRECTION OF IRON DEFICIENCY ANEMIA IN FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME IN INFANTS

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The state of iron metabolism in infants with food protein-induced enterocolitis syndrome was determined and the efficacy and safety of ferrous bisglycinate chelate for the correction of iron deficiency anemia in this group of children were studied. 40 children aged 6 months to 3 years with a chronic food protein-induced enterocolitis syndrome were examined. Signs of iron deficiency anemia were found in 80% of children. Administration of ferrous bisglycinate chelate at a dose of 0.5 mg of elemental iron/kg/day for 1 month contributed to the normalization of red blood cells and iron metabolism in the organism, which testified to the high bioavailability and effectiveness of this form of ferrous iron in chronic inflammatory processes in the intestine.

Key words: infants, food protein-induced enterocolitis syndrome, iron deficiency anemia, ferrous bisglycinate chelate.

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ОСОБЛИВОСТІ ДІАГНОСТИКИ ТА КОРЕКЦІЇ ДЕФІЦИТУ ЗАЛІЗА ПРИ ІНДУКОВАНОМУ ХАРЧОВИМИ БІЛКАМИ ЕНТЕРОКОЛІТИЧНОМУ СИНДРОМІ У ДІТЕЙ РАННЬОГО ВІКУ

Визначено стан обміну заліза у дітей раннього віку з індукованим харчовими білками ентероколітичним синдромом та досліджена ефективність і безпека застосування хелату бісгліцінату заліза для корекції залізодефіцитних станів у даного контингенту дітей. Обстежено 40 дітей віком від 6 місяців до 3 років з хронічним перебігом білок індукованого ентероколітичного синдрому. У 80% дітей було виявлено ознаки дефіциту заліза в організмі. Призначення хелату бісгліцінату заліза в дозі 0,5 мг елементарного заліза/кг/добу протягом 1 місяця сприяло нормалізації показників червоної крові та метаболізму заліза в організмі, що свідчило про високу біодоступність та ефективність застосування цієї форми двовалентного заліза за умов хронічного запального процесу в кишечнику.

Ключові слова: діти раннього віку, індукований харчовими білками ентероколітичний синдром, залізодефіцитні стани, хелат бісгліцінату заліза.

The work is a fragment of the research project "To study the pathogenetic mechanisms of the formation of allergic lesions in the gastrointestinal tract in young children" (state registration No. 0117U004534)

All over the world there is a rapid increase in the prevalence of allergic diseases, which often debut at a young age in the form of food-related reactions [1, 2]. Clinical manifestations of food allergy can be observed from various organs and systems, but in 47-65% cases [3], gastrointestinal tract (GIT) is the effector organ, which is in direct contact with allergens. These manifestations of food allergy have common features of pathogenesis, but are differentiated by the main clinical manifestations: delayed vomiting, the presence of blood in the stool and chronic diarrhea. Pathogenesis similarity is manifested in the presence of mainly eosinophilic inflammation of certain parts of the gastrointestinal tract, which leads to increased permeability of the intestinal wall, damage to the cilia, localized aphthous ulcers and nodular lymphoid hyperplasia [4].

Food protein-induced enterocolitis syndrome (FPIES), which develops as a result of cell-mediated immune mechanisms, is common at an early age and is clinically characterized by vomiting after ingestion of causative products and diarrhea with mucus and/or blood, which can lead to dehydration and hypotension [5]. The first symptoms of FPIES manifest at the age of 2 to 7 months, when a formula or complementary foods are added to the child's diet. The most common causal products of FPIES are dairy products and soy formulas, but there are reports that eating solid these foods: rice, oats, eggs, barley, potatoes, chicken, turkey, peas, bananas, fish, mutton and corn can also cause FPIES [6].

The results of clinical observations indicate a high frequency of iron deficiency anemia in the intestinal diseases, which occur as a result of impaired iron absorption and its loss in diarrheal syndrome. In turn, limiting the food ingestion due to long-term elimination diets leads to alimentary supply deficiency of the child's organism with iron and other nutrients involved in iron metabolism [2, 13].

Epidemiological studies linking allergies to iron deficiency anemia have emerged in the last decade. Immune activation in the conditions of iron deficiency anemia leads to the expansion of Th2- but not Th1 cells, which can cause class switching in B cells and prevents the proper activation of M2 but not M1 macrophages. Moreover, many allergens, in particular lipocalin, may be able to indirectly bind iron by siderophores containing catechol fragments. Locally limited iron deficiency anemia can result in the Th2 cells generation during immune activation and thus prepare for allergic sensitization.

In pediatric practice, especially in infants, ferric iron drugs are more commonly used today, but understanding the benefits of ferrous iron drugs in terms of therapeutic effect and duration of treatment requires finding ferrous iron drugs with good tolerability and minimal irritation to the gastrointestinal tract.

In this regard, the innovative form of ferrous iron – ferrous bisglycinate chelate, in which one molecule of iron is connected with carboxyl groups of two molecules of glycine by means of covalent bonds, attracts an attention. Experimental studies have shown that the ferrous chelate compound is not hydrolyzed in the stomach; it is completely absorbed in the small intestine and invariably enters the cytoplasm of enterocytes, where the iron molecule is released [12].

This absorption mechanism provides a very high bioavailability of bisglycinate chelate among iron compounds – the use of iron bisglycinate chelate at a dose of 0.75 mg/kg/day has shown efficacy against the hematopoietic response comparable to iron sulfate at a dose of 3 mg/kg/day. [7]. Higher bioavailability of bisglycinate chelate leads to lower iron burden, avoids iron overload and potential side effects with equivalent efficacy.

There are few references in the available literature on the problems of iron deficiency anemia in allergic intestinal diseases, which determines the relevance of this study.

The purpose of the study was to determine the state of iron metabolism in infants with food protein-induced enterocolitis syndrome and study the efficacy and safety of ferrous bisglycinate chelate for the correction of iron deficiency anemia in this group of children.

Materials and methods. In the Department of Nutrition and Somatic Diseases of Young Children of SI "Institute of Pediatrics, Obstetrics and Gynecology of the NAMS of Ukraine" we examined 40 children aged 6 months to 3 years with chronic food protein-induced enterocolitis syndrome (FPIES). FPIES was diagnosed on the basis of Recent International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome, developed by a working group of the American Academy of Allergy, Asthma and Immunology (AAAAI) in 2017. Clinical data, efficacy from food elimination, and recovery of gastrointestinal symptoms after an oral food challenge test with a causative allergen were considered. Additional confirmation of the diagnosis were the results of endoscopic examination with hemorrhagic colitis syndrome with targeted biopsy of the intestinal mucosa and its pathomorphological characteristics.

To assess the state of iron metabolism in the body, a hematological examination of children was performed to determine the following indicators: hemoglobin (HGB), red blood cells (RBC), hematocrit (HCT), color index, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW-CV), serum iron (SI), total iron-binding capacity (TIBC), transferrin saturation (TS) coefficient, serum ferritin (SF).

Subsequent studies included 32 patients with iron deficiency anemia. Of these, the 1st group included 15 children with iron deficiency anemia (IDA), the 2nd group – 17 children with latent iron deficiency (LID).

Numerous clinical studies using bisglycinate chelate as a source of iron [12] have shown that infants and young children with iron deficiency tolerate dietary supplements in doses providing about 15 to 120 mg of iron per day or food enrichment in doses providing about 2 to 23 mg of iron per day. The indicated dosage of iron bisglycinate contributed to the normalization of hemoglobin and ferritin levels in the blood serum.

In a study involving 25 children aged 3-18 years with celiac disease and iron deficiency, a test for absorption of oral ferrous bisglycinate chelate was performed. An increase in serum iron levels after 3 hours at least twice the baseline occurred in all but one patient [11].

Based on published studies, to correct iron deficiency in children of the 1st and 2nd groups, we prescribed ferrous bisglycinate chelate (TecnoFER Bambini) with 0.5 mg of elemental iron (2 drops/kg/day) for 1 month, according to the manufacturer's recommendations.

The correction effectiveness and the drug safety were evaluated on the basis of dynamic monitoring of patients and hematological examination to determine the indicators of iron metabolism in the dynamics of

supervision. All children completed a full course of TecnoFER administration. There were no cases of the early study withdrawal.

Statistical processing was performed using the standard Microsoft Excel software package. The significance of the differences was assessed using Student's t-test. The difference between the compared values was considered significant at $p<0.05$.

Results of the study and their discussion. Examination of children with FPIES revealed in most of them (32 children, 80.0%) clinical and laboratory signs of iron deficiency, including 15 patients with IDA (11 children – mild IDA, 4 children – moderate IDA). Almost half of the children with FPIES (17 patients – 42.5%) had no signs of anemia, but an in-depth hematological examination revealed LID.

All children with IDA (group 1) had hemoglobin levels below 110 g/l (mean 102.7±0.66 g/l), low hematocrit (29.7±0.25%), and color index (0.82±0.01). In group 2, 6 (35.3%) patients had hemoglobin within the age limit. A tendency to decrease hemoglobin (HGB = 110-115 g/l) was found in 11 (64.7%) children in this group. The mean hemoglobin index in Group 2 was 115.6±1.1 g/l. In some children of the 2nd group, a decrease in hematocrit and color index below the reference values was also found (in 8 and 11 patients, respectively).

In the clinical blood test, almost half of the patients of Group 1 (7 children-46.7 %) had a reduced red blood cell count (the mean index was 3.93±0.07 x 10^{12}/l, in 9 (60.0%) children changes in red blood cell indices were detected, which indicated the hypochromic nature of anemia (decrease in MCV, MCH, MCHC below reference values and increase in RDW-CV). In all children of Group 2, the number of red blood cells, MCV, MCHC and RDW-CV were within normal limits, while MCH (mean corpuscular hemoglobin) in a third of children was below the reference values, indicating iron deficiency in the body.

Analysis of iron metabolism in the examined children with FPIES showed the following.

TS coefficient, which is considered a sensitive marker of iron deficiency, was lower than the reference values in most children of both 1st and 2nd group: the mean value was 18.4±0.2% and 19.6±0.16, respectively. %.

Decreases in serum iron below the reference values were found in most children with FPIES, including 12 children in group 1 and 13 children in group 2. The mean serum iron level in the groups was approximately the same (group 1 – 5.3±0.6 μmol/l, group 2 – 5.9±0.5 μmol/l, $p>0.05$).

It is noteworthy that such an indicator of iron metabolism as the total iron binding capacity in the majority (87.5%) of children with FPIES was within the normal range. Only in 4 patients of the 1st and 2nd groups increase in the total iron-binding capacity was revealed. As is known, iron deficiency conditions are characterized by an increased level of total iron-binding capacity, while cytokine-induced anemia of chronic diseases is characterized by a decrease in this index.

Ferritin levels, which according to current clinical protocols are considered a marker of iron deficiency, were within normal limits (up to 200 ng/ml) in the vast majority of children. Decreased ferritin levels (less than 20 ng/ml) were found in 3 children of group 1. Most likely, this result can be explained by the features of iron deficiency in conditions of chronic inflammation of the intestine.

The presence of clinical signs of iron deficiency, low iron content in the diets of children with food protein-induced enterocolitis syndrome, was the basis for the iron supplements prescription. The results of the examination of children with IDA and LID in the dynamics of ferrous bisglycinate chelate administration are presented in the table 1.

According to the analysis of the results of the study, in children of the 1st group who received ferrous bisglycinate chelate to correct anemia, the dynamics showed a significant increase in hemoglobin, hematocrit, serum iron and transferrin saturation, as well as the tendency to increase the color index and normalization of red blood cell indices, which indicated a good therapeutic effect and increased iron reserves in the body. After treatment with ferrous bisglycinate chelate in most children of group 1, the hemoglobin level increased to ≥110 g/l, hematocrit to ≥ 35.0%. Only 4 children of the 1st group had laboratory signs of mild anemia.

Table 1

Red blood cells and iron metabolism indices in children with iron deficiency in the dynamics of treatment with ferrous bisglycinate chelate, M±m

Index	IDA, n = 15		LID, n = 17	
	Before administration	After administration	Before administration	After administration
HGB, g/l	102.7±0.66	114.3±0.59*	115.6±1.1	123.6±1.3 *
RBC, x 10^{12}/l	3.93±0.07	4.21±0.06	4.68±0.08	4.87±0.06

HCT, %	29.7±0.25	36.8±0.18*	31.5±0.24	37.1±0.16*
Color index	0.82±0.01	0.87±0.02	0.85±0.01	0.93±0.01*
MCV, fl	76.5±0.81	85.7±0.86	80.1±0.74	88.5±0.9
MCH, pg	24.8±0.27	27.9±0.3	23.2±0.24	28.8±0.21*
MCHC, g/l	273.2±3.0	296.4±2.5	326.2±2.8	321.8±3.1
RDW–CV, %	15.2±0.21	14.7±0.31	14.5±0.17	14.7±0.13
SI, umol/l	5.3±0.6	9.2±1.0*	5.9±0.5	13.3±0.11*
TIBC, umol/l	72.6±0.08	77.0±0.06	82.3±0.9	75.2±0.08
TS coefficient, %	18.4±0.2	26.9±0.24*	19.6±0.16	28.5±0.21*
SF, ng/mL	105.1±2.6	112.0±1.4	96.7±1.7	103.8±1.5

Note: – significant difference between the indices in the dynamics of administration ($p<0.05$).

Determination of iron metabolism in children of group 2 in the dynamics of the ferrous bisglycinate chelate administration showed a significant increase in serum iron levels and transferrin saturation. In 12 (70.6%) children of the 2nd group after a 1-month course of treatment, these indices increased to the age normal values. The obtained results indicate high bioavailability of this form of ferrous iron even under the conditions of malabsorption and maldigestion in allergic inflammation in the intestine.

In children who had iron deficiency after 1 month, treatment with ferrous bisglycinate chelate was continued.

Clinical observation of children treated with ferrous bisglycinate chelate showed a decrease in signs of iron deficiency – in most children there is a decrease in fatigue, irritability, increased physical activity, improved appetite and sleep, restoration of normal skin and mucous membrane colours.

All children tolerated ferrous bisglycinate chelate well. There were no cases of occurrence or exacerbation of dyspeptic symptoms (nausea, vomiting, abdominal pain, and diarrhea), allergic rash in response to the drug.

Therefore, the signs of latent iron deficiency and anemia found in patients with food protein-induced enterocolitis syndrome confirm the widespread of iron deficiency in allergic diseases. In particular, the British study of children with atopic eczema, the Korean study of iron content in young children with atopic dermatitis [1, 8, 9]. Most likely, the relationship between atopic diseases and anemia is multifactorial. In allergic intestinal lesions, the alimentary factor plays a significant role: long-term elimination diets and exclusion from the diet of important foods inevitably leads to a deficiency of alimentary supply of iron and other nutrients involved in iron metabolism. In some cases, iron losses in excess of physiological levels (in hemorrhagic colitis syndrome) are also important for the development of iron deficiency.

Given the pronounced negative impact of iron deficiency, especially at an early age, the modern view of the problem of iron deficiency in young children requires the timely diagnosis and active treatment of not only IDA but also latent iron deficiency. Given the difficulty of LID detection, in-depth hematological examination (determination of iron metabolism) of children at risk for the development of iron deficiency, including chronic intestinal diseases, is necessary. Treatment of iron deficiency conditions involves, first of all, a fairly long-term consumption of iron supplements. Iron supplements used in pediatric practice must have high bioavailability and good absorption, provide a rapid therapeutic effect, have sufficient safety and ease of dosing, minimal toxicity and irritation to the child's intestines, have a liquid release form (liquid, syrup, drops). High bioavailability of the chelated form of iron not only provides a rapid therapeutic effect when used, but also allows being limited to significantly lower (3-4 times) doses of oral iron in the treatment of iron deficiency, which is important to prevent overburden of the child's body with iron. An important feature of the ferrous bisglycinate metabolism is a double mechanism of absorption (binding to DMT-1 receptors, which are located on the villi of the duodenum, and PEPT-1 receptors, which are localized throughout the digestive tract). This mechanism of absorption ensures ferrous bisglycinate effectiveness in children with chronic diseases of the upper intestine, which are accompanied by damage to enterocytes and malabsorption syndrome [10, 11]. The absence of ferrous bisglycinate hydrolysis in the stomach and the absorption of this form of ferrous iron in unchanged form by enterocytes ensures the absence of free iron molecules that have a toxic and irritating effect on the gastrointestinal mucosa. This leads to a high level of safety and minimizes possible adverse reactions from the gastrointestinal tract when using ferrous bisglycinate chelate, which has been confirmed by clinical studies [12].

Conclusion

According to the study results, in 80% of children with a chronic form of food protein-induced enterocolitis syndrome were revealed signs of iron deficiency in the body, including 42.5% – latent iron deficiency, which confirms the need for an in-depth hematological examination (to determine the indices of iron metabolism) of this contingent of children in order to timely identify and correct iron deficiency in the early stages.

The most informative indicators of iron deficiency in allergic intestinal lesions in children are the transferrin saturation coefficient and serum iron levels.

Administration of ferrous bisglycinate chelate at a dose of 0.5 mg of elemental iron/kg/day for 1 month contributed to the normalization of red blood cells and iron metabolism in the organism. In any case there were no adverse reactions from the gastrointestinal tract or allergic reactions, which allow us to recommend it for the iron deficiency correction in allergic intestinal diseases in young children. The treatment course duration is determined individually depending on the dynamics of hematological parameters.

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