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CHARACTERISTICS OF IRON DEFICIENCY IN CHILDREN WITH CELIAC DISEASE

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ХАРАКТЕРИСТИКА ЖЕЛЕЗОДЕФИЦИТНЫХ СОСТОЯНИЙ У ДЕТЕЙ С ЦЕЛИАКИЕЙ

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The iron deficiency (ID) structure was estimated in 235 children with celiac disease aged eight months to 18 years. The patients included in the study were divided into three groups: group I included 64 (27.2 %) children without ID, group II – 106 (45.1 %) children with latent iron deficiency (LID), and group III – 65 (27.7 %) with iron deficiency anemia (IDA). In the period of manifestation of celiac disease, ID conditions were diagnosed in 72.8 % of cases. At the same time, LID dominated the structure of ID forms in all age groups. It was found that in children with celiac disease complicated by IDA, there was a lag in the pace of physical development, as well as more pronounced gastrointestinal symptoms: vomiting was noted more often (p=0.022), bloating (p=0.027) and diarrhea (p=0.018), than in the group I. Total atrophy of the small intestine mucosa villus predominates in 87.7 % of patients with IDA. Thus, specialized laboratory and instrumental methods of diagnosing celiac disease in children should include a detailed analysis of ID.

Keywords: iron deficiency anemia, atrophy of the small intestine mucosa, celiac disease, children

Проведена оценка структуры железодефицитных состояний у 235 детей с целиакией в возрасте от 8 месяцев до 18 лет. Пациенты, вошедшие в исследование, распределены на 3 группы: 64 (27,2 %) ребенка без железодефицитных состояний (I группа), 106 (45,1 %) детей с латентным дефицитом железа (II группа) и 65 (27,7 %) с железодефицитной анемией (III группа). В периоде манифестации целиакии железодефицитные состояния диагностированы в 72,8 % случаев. При этом во всех возрастных периодах в структуре форм дефицита железа преобладал латентный дефицит железа. Выявлено, что у детей с целиакией, осложненной железодефицитной анемией, отмечалось отставание темпов физического развития, а также более выраженная гастроинтестинальная симптоматика: чаще отме-

чались рвота (p=0,022), вздутие живота (p=0,027), диарея (p=0,018), чем в I группе. Тотальная атрофия ворсинок слизистой оболочки тонкой кишки превалирует у 87,7 % пациентов с железодефицитной анемией. Таким образом, наряду со специализированными лабораторно-инструментальными методами диагностика целиакии у детей должна включать детализированный анализ дефицита железа.

Ключевые слова: железодефицитная анемия, атрофия слизистой оболочки тонкой кишки, целиакия, дети

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BMI – body mass index
ESPGHAN – European Society for Pediatric Gastroenterology, Hepatology and Nutrition
HGB – hemoglobin
ID – iron deficiency
IDA – iron deficiency anemia
IDS – iron deficiency state
ITF – iron transferrin saturation coefficient
LID – latent iron deficiency
Me – median
MMSI – mucous membrane of the small intestine
SF – serum ferritin
SI – serum iron
TF – transferrin
TIBC – total iron-binding capacity

Celiac disease has increased in the pediatric population in recent decades, but up to 80–90 % of patients with this disease can go unnoticed for a long time. One of the main reasons for this is the pathomorphosis of clinical manifestations of coeliac disease – currently, at least 60 % of patients are diagnosed with intestinal symptoms, the proportion of asymptomatic and latent forms has increased significantly with the formation of subclinical deficiency conditions, various haematological patterns [1–4].

Iron deficiency anemia (IDA) is a polyetiological disease, which is characterized by a decrease in the level of iron in the body due to many reasons: impaired intake from food, absorption in the intestine, or increased losses. IDA takes 1st place in the Russian Federation among all anemias characteristic of childhood (70–80 %) [5, 6].

In 2019, IDA was recognized by the World Health Organization as the most common anemia in pediatric practice: its occurrence in different countries ranges from 7.8 % to 39.3 %. According to the literature, the peak incidence of IDA is the highest in two age periods: from 1 year to 3 years – 15 %, and from 11 to 15 years – 13 % in boys and 33 % in girls [7–10].

The development of iron deficiency states (IDS) in celiac disease is due to iron malabsorption since most of the iron (about 90 %) is absorbed in the duodenum, and the remaining 10 % in the proximal small intestine. And in celiac disease, toxic gluten peptides initiate an autoimmune process leading to apoptosis of enterocytes, which is accompanied by the development of atrophic changes in the mucous membrane of the small intestine (MMSI), impaired iron absorption with the formation of IDS [11–13].

The most common variant of celiac anemia is IDA; in 40 % of cases, it may be the only extraintestinal manifestation of the disease, significantly complicating the diagnostic search. The detection rate of IDS among newly diagnosed patients with celiac disease ranges from 12 to 85 %. Children with celiac disease are at risk for developing IDA. According to literature data, among children with anemia participating in a study in India, the diagnosis of celiac disease is established in 5.4 %, and most often (about 28.4 %) – in patients with anemia resistant to iron therapy [7, 12, 14].

The study aimed to assess clinical, anamnestic, and laboratory-instrumental features of the course IDS in children with coeliac disease in the acute period.

Material and Methods. A study based on City Children's Clinical Hospital named after G. K. Filippsky (Stavropol, Russia) included children aged eight months to 18 years (the average age was 5.0±0.3 years). Patients were examined from 2001 to 2022, and the diagnosis of celiac disease was verified by the ESPGHAN criteria (1990, 2012, 2020) [15].

The criteria for the diagnosis of IDA was the level of hemoglobin (HGB) in girls over 12 years of age, which is less than 120 g/l; in boys over 12 years of age – less than 130 g/l, at the age of 5 to 12 years – less than 115 g/l, and in children from 3 months to 5 years – 110 g/l; with a combined decrease in serum ferritin (SF) below 30 μg/l, serum iron (SI) below 12.5 μmol/l, iron transferrin saturation coefficient (ITF) less than 17 % (calculated according to the formula ITF = (ST/ITBC)x100) and a simultaneous increase in the total iron-binding capacity of serum (TIBC) more than 69 μmol/l and transferrin (TF) more than 3.6 g/l [6]. With an HGB level exceeding the above parameters and a combined decrease in SF below 30 μg/l and SI below 12.5 μmol/l, a diagnosis of latent iron deficiency (LID) was made [6].

During the study, three groups were formed, taking into account the presence of the IDS variant. The I group included 64 (27.2 %) children without IDA, the II group included 106 (45.1 %) patients with LAD, and the III group had 65 (27.7 %) children with IDA.

The total number of WHD in children in the period of manifestation of celiac disease was 72.8 %. In the structure of IDA, anemia of the 1st degree (HGB <110–120 g/l in girls, <110–130 g/l in boys) was detected in 50 (77.0 %), 2nd degree (HGB <89 g/l) – in 14 (21.5 %), III degree (HGB <70 g/l) – in 1 (1.5 %) child.

Depending on the age of diagnosis verification, children are divided into groups: infant (0–1 years old), pre-preschool (1–3 years old), preschool (3–7 years old), junior school (7–12 years old), and senior school (over 12 years old) age.

All patients underwent a morphological study of the TLS – verification of villous atrophy of more than Marsh stage 3A was assessed in favor of the diagnosis of celiac disease [16]. The analysis of anthropometric indicators was carried out using the WHO AnthroPlus and MedScape software(https://www.who.int/tools).

Quantitative characteristics are presented as mean values and standard error (M±m). Sets of quantitative indicators of non-parametric quantitative data were described using the importance of the median (Me), the first and third quartiles [Q1; Q3]. Significant differences between groups of parametric quantitative data were determined using Student's t-test. The nominal data were described with absolute and relative (%) values. The analysis of nominal data was carried out using the Pearson test (χ^2). Statistical data processing was done using the program SPSS Statistics 24 (IBM, USA). Differences were considered statistically significant at $p<0.05$.

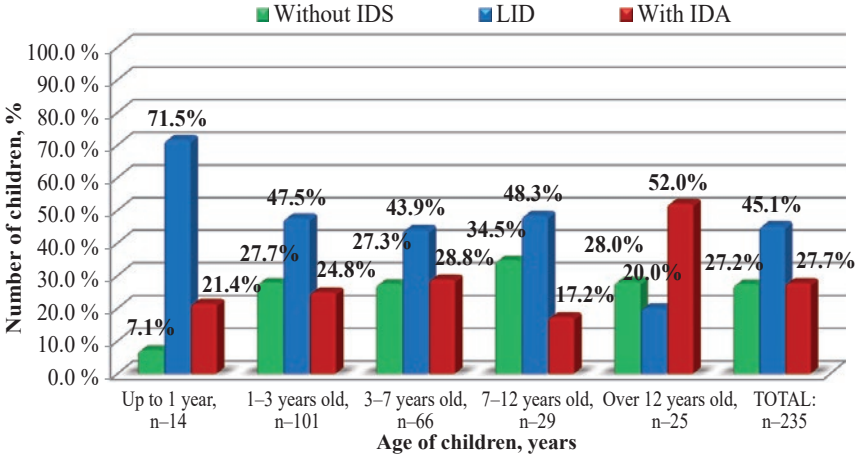

Fig. Frequency of children with IDA, LID and without IDS, examined in the active period of celiac disease, depending on the age at diagnosis

Results and Discussion. The study included 235 children with an established diagnosis of celiac disease, whose average age was 5.0±0.3 years, revealed a predominance of girls – 131 (55.7 %) over boys – 104 (44.3 %). Patients with classic gastrointestinal manifestations were 202 (86.0 %) children, children with dominant extraintestinal symptoms – 33 (14.0 %). The median age of manifestation of complaints in the analyzed groups of children did not differ significantly: in the group without IDS – 1.0 [0.6; 3.0] year; with LID – 1.0 [0.5; 2.4] year, with IDA – 1.2 [0.5; 3.0] years. At the same time, the age of celiac disease diagnosis verification in the group I was 3.4 [2.0; 7.7] years, in the group II it is somewhat less – 2.7 [2.0; 5.2] years, and in the group III – 4.8 [1.8; 7.1] years.

The ID was recorded in 90 (68.7 %) girls and 81 (77.9 %) boys, while the frequency of IDA in girls 38 (29.0 %) slightly exceeded that in boys – 27 (26.0 %).

According to the data shown in Figure, the number of cases of IDA in children diagnosed at the age of over 12 years (52.0 %) exceeds the number of patients diagnosed at the age of 7 to 12 years (17.2 %) by 3.0 times (p=0.007), in infants – 2.4 times (p=0.063), in pre-school – 2.1 times (p=0.008), and in pre-school – 1, 8 times (p=0.039), respectively.

In patients with celiac disease complicated by IDA, lower values of physical development parameters were recorded: the frequency of somatogenic nanism (Z-score of growth (from –2.0 SDS and less) occurs 2.0 times more often than in the group without IDS (p=0.015). A direct correlation was found between IDS and underweight (r=0.17, p=0.008), as well as growth retardation (r=0.23, p=0.001).

When analyzing the clinical picture, the «major» (main) and «small» (minor) symptoms are distinguished (Table 1). According to this data, it was found that in patients with IDA, compared with the group of children without IDS, gastrointestinal symptoms were more pronounced: vomiting was observed more often by 1.9 times (p=0.022), abdominal distention – by 1.5 times (p=0.027), diarrhea – 1.5 times (p=0.018). Among extraintestinal manifestations in children with IDA, growth retardation by 1.6 times (p=0.011) and sleep inversion – by 2.8 times (p=0.028), respectively, was significantly more common. The frequency of other symptoms did not differ significantly.

Table 1

Clinical picture of celiac disease in children, depending on the presence and form of ID

Symptoms of celiac disease		The presence and form of iron deficiency			Significance of differences (χ^2)		
		Without IDS, n=64	LID, n=106	with IDA, n=65	P_1	P_2	P_3
«Big» symptoms	Bloating	23 (35.9 %)	51 (48.1 %)	36 (55.4 %)	0.121	0.027	0.356
	Vomit	12 (18.8 %)	21 (19.8 %)	24 (36.9 %)	0.866	0.022	0.014
	Diarrhea	28 (43.8 %)	57 (53.8 %)	42 (64.6 %)	0.206	0.018	0.113
	Recurrent abdominal pain	33 (51.6 %)	50 (47.2 %)	33 (50.8 %)	0.579	0.929	0.648
	Decreased appetite	27 (42.2 %)	52 (49.1 %)	28 (43.1 %)	0.385	0.919	0.447
	Underweight	35 (54.7 %)	69 (65.1 %)	45 (69.2 %)	0.178	0.089	0.578
	Growth retardation	26 (40.6 %)	62 (58.5 %)	41 (63.1 %)	0.024	0.011	0.552
	Irritability	14 (21.9 %)	34 (32.1 %)	23 (35.4 %)	0.153	0.09	0.656
«Minor» symptoms	Constipation	10 (15.6 %)	18 (17.0 %)	5 (7.7 %)	0.818	0.16	0.084
	Ossalgia	3 (4.7 %)	4 (3.8 %)	4 (6.2 %)	0.772	0.714	0.475
	Caries	1 (1.6 %)	3 (2.8 %)	2 (3.1 %)	0.598	0.569	0.926
	Allergic skin rashes	16 (25.0 %)	34 (32.1 %)	14 (21.5 %)	0.327	0.642	0.137
	Cerebralgia	4 (6.3 %)	5 (4.7 %)	8 (12.3 %)	0.666	0.237	0.07
	Sleep inversion	5 (7.8 %)	20 (18.9 %)	14 (21.5 %)	0.049	0.028	0.672

Note: P_1 – significance of differences in the compared groups of children without ID and with LID; P_2 – significance of differences in the compared groups of children without ID and with IDA; P_3 – significance of differences in the compared groups of children with LID and IDA.

Table 2 analyses the relationship between the laboratory ferritin status and the mucosal atrophy stage in the analyzed groups of children in the acute period of coeliac disease. These data show that, as mucosal atrophy increases in children, concentrations of transport and iron laboratory markers decrease during the acute coeliac period.

Table 2

Ferritin status indicators of iron metabolism in children with celiac disease, examined in the active period, depending on the stage of small intestinal mucosal atrophy

Hemogram indicators	Stages of atrophy of SOTK according to the classification Marsh – Oberhuber			Reliability differences		
	3A, n=48	3B, n=62	3C, n=125	P_1 3A/3B	P_2 3A/3C	P_3 3B/3C
Hb, g/l	131.8±1.6	125.2±1.4	111.9±1.6	0.002	0.001	0.001
RBC, 10^{12}/l	4.7±0.1	4.6±0.1	4.4±0.1	0.481	0.035	0.159
MCV, fl	80.0±0.4	78.2±0.7	73.8±0.6	0.028	0.001	0.001
MCH, pg	26.9±0.2	26.3±0.4	24.3±0.3	0.183	0.001	0.001
MCHC, g/dl	343.2±1.3	339.8±1.7	329.0±1.5	0.115	0.001	0.001
RDW, %	13.1±0.2	13.9±0.3	18.3±1.6	0.029	0.002	0.007
SI, μmol/l	12.6±0.7	11.7±0.6	8.0±0.4	0.331	0.001	0.001
SF, μg/l	32.6±2.9	31.3±2.4	16.7±1.6	0.731	0.001	0.001
TIBC, μmol/l	62.6±1.5	62.4±1.5	73.0±0.8	0.925	0.001	0.001
TFR, g/l	3.0±0.1	3.1±0.1	3.5±0.1	0.481	0.001	0.005
ITF, %	21.7±1.5	20.3±1.3	11.8±0.7	0.482	0.001	0.001

Note: P_1 – significance of differences in the analyzed groups of children with Marsh – Oberhuber stage 3A and 3B; P_2 – significance of differences in the analyzed groups of children with Marsh – Oberhuber stage 3A and 3C; P_3 – significance of differences in the analyzed groups of children with Marsh – Oberhuber stage 3B and 3C.

In children with celiac disease complicated by IDA, the stage of atrophy of the MMSI Marsh 3C predominates and amounts to 57 (87.7 %) of 65 children, which is significantly 3.7 times (p=0.001) more often than in the group of patients without IDS, and in 1.7 times (p=0.001) more often than in the group of children with LV.

Conclusion. The study demonstrates that among patients in the acute period of celiac disease, IDS are detected much more often (72.8 %) than in the population. This condition is characteristic of all ages but is most pronounced during intensive growth and vulnerability in iron supply (in the first year of life and at puberty).

There were differences in the incidence of celiac disease in patients with IDA, ID, and without IDS: patients with IDS have more gastrointestinal symptoms and lower physical development than children without IDS. It has been found that the gradual depletion of the transport and tissue pool of iron in children accompanies the increase in atrophic processes in MMSI.

Thus, diagnosis of celiac disease in children, along with specialized laboratory and instrumental methods, should include a detailed analysis of laboratory criteria for identification IDS. Children with ID at any age are at risk for serological screening for coeliac disease.

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CLINICAL FEATURES AND OUTCOMES OF MENINGITIS FOR CHILDREN IN THE REPUBLIC OF NORTH OSSETIA–ALANIA

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КЛИНИЧЕСКИЕ ОСОБЕННОСТИ И ИСХОДЫ МЕНИНГИТОВ У ДЕТЕЙ В РЕСПУБЛИКЕ СЕВЕРНАЯ ОСЕТИЯ–АЛАНИЯ

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The study was to determine regional characteristics and outcomes of meningitis in 105 children. Purulent meningitis developed in young children (56.7 %) and was accompanied by severe (85.1 %) forms, risks of infectious (29.9 %) and neurological (20.9 %) complications, and a protracted course (65.7 %). Children with serous meningitis had an underlying