CHALLENGES IN DIFFERENTIAL DIAGNOSIS OF COELIAC DISEASE AND GLUTEN INTOLERANCE IN CHILDREN

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Summary

Introduction. *The group of gluten-dependent diseases currently comprises 3 pathological conditions: celiac disease, non-celiac gluten intolerance and wheat allergy. Celiac disease is a chronic, immune-inflammatory disease that occurs in genetically predisposed individuals in response to exposure to the main cereal protein - gluten. It is characterised by damage to the small intestinal mucosa, leading to its atrophy with corresponding intestinal and extraintestinal clinical manifestations. The treatment is a lifelong gluten-free diet. Gluten intolerance is a condition characterised by the onset of irritable bowel syndrome-like symptoms within hours or days of eating gluten-containing foods. These symptoms disappear quickly when the consumption of gluten-containing products is stopped. The causes of gluten intolerance are amylase inhibitors, trypsin and fructans (FODMAPS), which are present in wheat and other gluten-containing and gluten-free foods. New recommendations from the European Society of Paediatrics, Gastroenterology, Hepatology and Nutrition (ESPGHAN) for the diagnosis of celiac disease in children were published in 2020. The diagnosis of gluten intolerance requires the exclusion of celiac disease and wheat allergy.*

The aim of the study *was to determine the characteristics of the clinical course of celiac disease and gluten intolerance (analysis of intestinal and extraintestinal symptoms), serological and morphological features for differential diagnosis and management.*

Material and methods. *Thirty children aged 9 months to 11 years were included in the study for the period 2016-2023. Distribution by gender: 13 (43.3%) boys and 17 (56.6%) girls, p=0.1391. Patients were divided into two groups according to the diagnosis of celiac disease and gluten intolerance. The study included a detailed medical history, assessment of the child's examination and physical development. Determination of titer of IgA antibodies, IgA to tissue transglutaminase (tTG-IgA), endomysial IgA (EMA-IgA), gliadin IgG, wheat IgE antibodies, endoscopy and morphological examination of duodenal mucosal biopsies. Descriptive analysis and comparison of two proportions were used. Non-parametric methods were used to test hypotheses. Logistic regression analysis using the relative risk index (RR) and its 95% confidence interval (CI). Differences in parameters were considered statistically significant when p<0.05.*

The study was approved by the Commission on Biomedical Ethics for Compliance with Moral and Legal Rules of Medical-Scientific Research of the Kharkiv National Medical University. It was confirmed that the research does not contradict the basic bioethical norms and complies with the main provisions of the Good Clinical Practice (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (04.04.1997), the Declaration of Helsinki of the World Medical Association on the ethical principles of research involving human subjects (1964-2008), and the Order of the Ministry of Health of Ukraine No. 690 (23.09.2009) with amendments according to the Order of the Ministry of Health of Ukraine No. 523 (12.07.2012). Both parents of the patients were informed about the purpose and procedures of the research and signed the informed consent for their children's participation in this study.

Statistical analysis was performed using Statistica 7.0 StatSoft Inc.1984-2004, (serial number 1225555555, USA) and MedCalc version 14.8-© 1993-2014 MedCalc Software bvba (Acacialaan 22 B-8400 Ostend, Belgium). The procedures, logic and interpretation of the statistical parameters obtained in the mathematical and statistical analysis were based on generally accepted rules of medical and biological statistics. Descriptive analysis and comparison of two proportions were used. Non-parametric methods were used to test hypotheses: Logistic regression analysis using the relative risk index (RR) and its 95% confidence interval (CI). Differences in parameters were considered statistically significant if p<0.05. Patients in the study were divided into two groups according to the diagnosis of celiac disease and gluten intolerance.

The presented article is a fragment of the scientific research of the Department of Paediatrics No.1 and Neonatology of the Kharkiv National Medical University: topic "Medical and social adaptation aspects of children with somatic pathology in modern conditions"; state registration No.0120U102471.

Results. *66.6% of children from the general cohort were diagnosed with celiac disease and 33.3% of children with gluten intolerance, p=0.0053. The mean age of the children with celiac disease was 8.4±1.0 years. Gender distribution of children with celiac disease - 50.0% boys, 50.0% girls, p=1.0000. The mean age of the children with gluten intolerance was 9.1±1.0 years. The gender distribution of children with gluten intolerance was 70.0% boys and 30.0% girls, p=0.0001. In 65.0% of children with celiac disease, the diagnosis was confirmed at an earlier stage than in children with gluten intolerance, p=0.0350. A family history of autoimmune pathology was found in 40% of children with celiac disease. All patients with celiac disease were seropositive for serological biomarkers. IgA to tissue transglutaminase tTG-IgA was detected in 95.0% of children with celiac disease (RR=20.4; 95% CI 1.4-307.2; p=0.0292).*

Diarrhoea and abdominal pain were found in 18/30 children from the general cohort (RR=0.8; 95% CI 0.4-1.4; p=0.5050), loss of appetite - in 17/30 children (RR=0.7; 95% CI 0.4-1.3; p=0. 2695), 15/30 children had constipation and poor weight

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gain (RR=0.7; 95% CI 0.3-1.5; p=0.4209), 14/30 children had delayed physical development and weakness (RR=0.9; 95% CI 0.4-1.9; p=0.7929). One third of the children had hyperactivity and attention deficit syndrome, sleep disturbances. All children with celiac disease had various stages of small intestinal mucosal atrophy according to the Marsh-Oberhuber classification. No atrophic changes in the small intestinal mucosa were found in children with gluten intolerance (normal structure of villi and crypts), but infiltrative changes were found in 60% of these patients (increase in intraepithelial lymphocytes).

Conclusion. Comparative analysis showed no significant differences in the clinical presentation of celiac disease and gluten intolerance. Autoimmune pathology was not found in the family history of children with celiac disease, whereas it was found in 40% of patients with celiac disease. The diagnosis of gluten intolerance is made in case of exclusion of family history of autoimmune nosology; absence of autoantibodies to tissue tranglutaminase and deaminated gliadin peptides, endomysial autoantibodies, which should be determined on a gluten-containing diet, and absence of specific IgE to wheat. All children with celiac disease had various stages of atrophy of the small intestinal mucosa according to the Marsh-Oberhuber classification, whereas no atrophic changes were found in children with gluten intolerance, but 60% of patients with gluten intolerance had infiltrative changes in the small intestinal mucosa.

Keywords: Celiac Disease; Gluten Intolerance; Gluten-free Diet; Children.

Introduction

Despite significant advances in medical science in the diagnosis and treatment of gastrointestinal diseases, the improvement of diagnostic algorithms for diseases of the small intestine is an issue of current interest. The diagnosis of celiac disease is not without its difficulties. Celiac disease remains one of the most difficult to diagnose, but the differential diagnosis between celiac disease and gluten intolerance is even more challenging.

The group of gluten-dependent diseases includes 3 pathological conditions:

1). Celiac disease (gluten enteropathy, nontropical sprue, Gi-Herter-Heibner disease, etc.) is a genetically determined autoimmune disease with predominant damage to the small intestine associated with gluten consumption. Celiac disease is characterised by a reversible atrophic enteropathy and the development of gluten-dependent clinical symptoms.

2). Gluten intolerance is a diagnosis of exclusion in patients with a negative reaction of the body to the consumption of gluten-containing products in the absence of pathological signs characteristic of celiac disease. Symptoms disappear after the introduction of a gluten-free diet and reappear when the patient resumes gluten consumption.

3). Wheat allergy: This disease develops as a type of IgE-mediated allergic reaction in response to the ingestion of gluten-containing products.

Celiac disease occurs in 0.5-1% of the population in most countries [1]. According to the public organization "Ukrainian Celiac Association", the number of patients with celiac disease in Ukraine is about 2,000 and it is increasing every year.

The risk of developing celiac disease is significantly increased in first- and second-degree relatives of patients with celiac disease, type 1 diabetes, selective IgA deficiency, autoimmune thyroiditis, Turner syndrome, Williams syndrome [2].

Celiac disease often remains undiagnosed due to clinical polymorphism and non-specific symptoms that appear between 6 and 24 months after the introduction of gluten-containing foods into the diet [3]. There may be a latency period between gluten ingestion and clinical manifestation. The main gastrointestinal symptoms of celiac disease are chronic diarrhoea, anorexia, abdominal pain and bloating, weight loss; some children may vomit. Symptoms are usually different in infants and older children. All of the gastrointestinal symptoms listed are common in children under the age of three, while abdominal pain is typical in older children. Celiac disease may be associated with diarrhoea (stools are often large and foul-smelling) or constipation. Common extraintestinal manifestations include delayed linear growth and puberty, chronic anaemia, osteopenia, osteoporosis, dental enamel defects, irritability, chronic fatigue, neuropathy, arthritis, arthralgia, amenorrhoea, elevated liver enzymes, increased risk of malignant neoplasms. Depending on the clinical phenotype, there are typical, atypical, subclinical, symptomatic and asymptomatic celiac diseases. Different manifestations and clinical polymorphisms complicate the differential diagnosis among gluten-dependent diseases. Therefore, the diagnosis of celiac disease is based on a complex of clinical, serological and anamnestic data.

The first stage - determination of total immunoglobulin IgA levels and IgA to tissue transglutaminase (tTG-IgA) on a gluten-containing diet.

Children with tTG-IgA titres less than 10 times the upper limit of normal should have a biopsy to confirm the diagnosis. If the tTG-IgA titer is more than 10 times the reference value, the diagnosis of celiac disease can be confirmed without biopsy if endomysial antibodies (EMA-IgA) are present in the second blood serum sample. In children with low levels of total IgA (<0.2 g/l in children older than 3 years), IgG to deaminated gliadin peptide (DGP), EMA or tTG should be determined. In children with low total IgA, the tTG-IgA test is invalid. In this case, IgG antibodies to tTG (tTG-IgG) and DGP-IgG should be determined [3]. If either or both of these IgG-based tests are elevated, the patient should be evaluated with an intestinal biopsy. Human leukocyte antigen (HLA) genetic testing is not mandatory in the case of a serologically confirmed diagnosis [4-7].

Endoscopy with biopsy of the small bowel mucosa is a separate diagnostic step. More than 4 biopsies should be taken from the distal part of the duodenum and more than 1 from its bulb. The modified Marsh classification is used to assess damage to the small intestinal villi in gluten-dependent cases. Children with very high tTG-IgA levels, positive anti-endomysial antibodies (EMA) and typical symptoms do not require biopsy. Intestinal biopsy is useful in the differential diagnosis of other gastrointestinal diseases [8, 9].

The aim of celiac disease therapy is to restore bowel function, normalise body weight and correct

deficiencies in essential nutrients [10, 11].

The pathogenetic treatment is a gluten-free diet to avoid the offending factor. It is necessary to follow a gluten-free diet for life. This leads to the disappearance of symptoms and normalisation of bowel activity.

Gluten is found in the following products: bread and all products made from wheat, rye, barley and oat flour, pasta, semolina. In small concentrations, gluten can be found in sausages and hot dogs, tinned meat and fish, mayonnaise and ketchup, various sauces, instant coffee and cocoa powder, chocolate, ice cream, soy products, instant soups, bouillon cubes, etc. Patients with newly diagnosed celiac disease should be screened for iron deficiency anaemia and vitamin D deficiency. As the gluten-free diet is associated with vitamin and trace element deficiencies, multivitamins are recommended.

While the patient is on a gluten-free diet, the specific serological test (tTG-IgA) should be repeated approximately every six months; if it becomes normal - annually. A decrease in the antibody titer indicates compliance with the diet and confirms the diagnosis of celiac disease [8].

A gluten-free diet should not be started before serological testing for celiac disease, as these tests can be false negative. In children with an inconclusive diagnosis, reintroduction of gluten is prescribed after a gluten-free diet. In patients on a gluten-free diet with persistent symptoms and histological abnormalities or increased titres of serum antibodies, it is necessary to exclude secondary lactose intolerance, irritable bowel syndrome, bacterial overgrowth in the small intestine, diseases associated with atrophy of the villi of the small intestine. Refractory celiac disease is very rare in children.

Gluten intolerance is the most common gluten-related syndrome, with a prevalence of 0.5% to 13% in the general population [12,13]. Diagnosis is made by excluding other gluten-related conditions such as celiac disease and wheat allergy in children with persistent intestinal/extraintestinal symptoms associated with gluten consumption. Gluten intolerance is not associated with autoimmune lesions of the small intestine, thyroid, pancreas, liver, etc. To confirm this diagnosis, the child is prescribed a gluten-free diet for at least 4 weeks, after which gluten is reintroduced. The rapid disappearance of symptoms on a gluten-free diet and their rapid reappearance on reintroduction of gluten confirms gluten intolerance.

The aim is to determine features of the course, serological and morphological features for differential diagnosis and management of celiac disease and gluten intolerance.

Material and methods

Our study included 30 children who were admitted between 2016 and 2023. Their age ranged from 9 months to 11 years. Gender distribution: 13 (43.3%) boys and 17 (56.6%) girls, p=0.1391.

The study included a detailed review of medical history, family history and analysis of medical records, evaluation of the child's examination, anthropometric measurements. Determination of total titer of IgA antibodies, tTG-IgA, EMA-IgA, gliadin-IgG. Allergy to wheat was excluded by evaluation of IgE antibodies to wheat. Endoscopy and biopsy were performed in children with tTG-IgA titres less than 10 times the upper limit of normal.

The study was approved by the Commission on Biomedical Ethics for Compliance with Moral and Legal Rules of Medical-Scientific Research of the Kharkiv National Medical University. It was confirmed that the research does not contradict the basic bioethical norms and complies with the main provisions of the Good Clinical Practice (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (04.04.1997), the Declaration of Helsinki of the World Medical Association on the ethical principles of research involving human subjects (1964-2008), and the Order of the Ministry of Health of Ukraine No. 690 (23.09.2009) with amendments according to the Order of the Ministry of Health of Ukraine No. 523 (12.07.2012). Both parents of the patients were informed about the purpose and procedures of the research and signed the informed consent for their children's participation in this study.

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Results

Demographic, clinical and laboratory characteristics of the children are shown in Table 1. In the general cohort, 20 (66.6%) children were diagnosed with celiac disease and 10 (33.3%) children had gluten intolerance, p=0.0053. The mean age of the children with celiac disease was 8.4±1.0 years. Gender distribution among children with celiac disease - 10 (50.0%) boys, 10 (50.0%) girls, p=1.0000. The mean age of the children with gluten intolerance was 9.1±1.0 years. The gender distribution among the children with gluten intolerance was 7 (70.0%) boys and 3 (30.0%) girls, p=0.0001.

In 13 (65.0%) children with celiac disease, the diagnosis was confirmed at an earlier stage than in children with gluten intolerance, p=0.0350.

All patients with celiac disease were seropositive for serological biomarkers. In 19 (95.0%) children with

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celiac disease, IgA to tissue transglutaminase tTG-IgA was detected (RR=20.4; 95% CI 1.4-307.2; p=0.0292). In 3 (30.0%) children with gluten intolerance, the level of IgG anti-gliadin antibodies was elevated (RR=1.0; 95% CI 0.3-3.2; p=1.0000), but IgA antibodies to tissue transglutaminase and endomysium were not detected in any of the children. Autoimmune pathology in the family history was found in 8 children with celiac disease, confirming an autoimmune mechanism in its development [14]. Antibodies to wheat were measured in 15 children from the general group: all results were negative. Allergy to wheat was therefore excluded.

Table 1

Demographic, clinical and laboratory data of children with coeliac disease and gluten intolerance, abs., (%)

Data	Children with celiac disease, n=20	Children with gluten intolerance, n=10	p
1-4 years	12 (60,0)	7 (70,0)	0,2181
4-7 years	6 (30,0)	2 (20,0)	0,2211
7-11 years	2 (10,0)	1 (10,0)	0,5000
Girls	10 (50,0)	3 (30,0)	0,1487
Boys	10 (50,0)	7 (70,0)	0,1487
Autoimmune pathology in the family history	8 (40,0)	0 (2,9)	0,0160
Positive Ig A to tTG	19 (95,0)	0 (2,9)	0,0001
Positive Ig G to gliadin	6 (30,0)	3 (30,0)	0,5000
Normal level of total Ig A	20 (100,0)	10 (100,0)	0,5000
Positive antibodies to endomysium (EMA-IgA)	6 (30,0)	0 (2,9)	0,1231
Negative antibodies to endomysium (EMA-IgA)	14 (70,0)	10 (100,0)	0,0350
Deficiency of 25-OH-D3	8 (40,0)	3 (30,0)	0,1367
Deficiency anaemia	12 (60,0)	4 (40,0)	0,0450
Constipation	8 (40,0)	3 (30,0)	0,1367
Diarrhoea	12 (60,0)	7 (70,0)	0,1419
Abdominal pain	9 (45,0)	4 (40,0)	0,3801
Abdominal bloating	13 (65,0)	6 (60,0)	0,2181
Loss of appetite	10 (50,0)	5 (50,0)	0,5000
Weakness	8 (40,0)	4 (40,0)	0,5000
Delay in physical development	9 (45,0)	5 (50,0)	0,2192
Sleep disturbances	5 (25,0)	3 (30,0)	0,2797
Psychomotor and speech development retardation	8 (40,0)	5 (50,0)	0,1487
Attention deficit hyperactivity disorder	6 (30,0)	3 (30,0)	0,5000

No significant differences were found in the comparative analysis of intestinal and extraintestinal manifestations in children with celiac disease and gluten intolerance (Figure 1). Diarrhoea and abdominal pain were found in 18/30 children of the general cohort (RR=0.8; 95% CI 0.4-1.4; p=0.5050), loss of appetite in 17/30 children (RR=0.7; 95% CI 0.4-1.3; p=0. 2695), 15/30 children had constipation and poor weight gain (RR=0.7; 95% CI 0.3-1.5; p=0.4209), 14/30 children had delayed physical development and weakness (RR=0.9; 95% CI 0.4-1.9; p=0.7929). One third of the children had attention deficit hyperactivity disorder and sleep disturbances.

Associated pathologies of children with celiac disease and gluten intolerance are the following: iron deficiency anaemia in 11/30 children (RR=1.3; 95% CI 0.4-3.9; p=0.6044), protein-energy deficiency in 9/30 children (RR=0.6; 95% CI 0.2-1.8; p=0.3908), irritable bowel syndrome - 8/30 children (RR=0.8; 95% CI 0.2-2. 8; p=0.7684), subclinical hypothyroidism - 3/30 children (RR=3.6; 95% CI 0.2-64.8; p=0.3752), chronic gastroduodenitis - 2/30 children (RR=2.6; 95% CI 0.1-49.9; p=0. 5220), chronic pancreatitis - 1/30 children (RR=1.6; 95% CI 0.1-35.4; p=0.7762), autism spectrum disorders - 1/30 children (RR=0.2;

95% CI 0.1-3.9; p=0.2724), (Fig. 2).

Morphological analysis of biopsies of the small intestinal mucosa was performed in 15 (50%) children with celiac disease and in 6 (60%) with gluten intolerance. All children with celiac disease had different stages of mucosal atrophy according to the Marsh-Oberhuber classification. No atrophic changes in the small intestinal mucosa were found in children with gluten intolerance (normal structure of villi and crypts), but infiltrative changes were found in 6 (60%) children (increase of intraepithelial lymphocytes).

We present our clinical cases for illustration.

Clinical case No.1

A 9-month-old girl was admitted to the pediatric gastroenterology department. The girl's mother complains of her daughter's lack of weight gain for 2 months, loose stools up to 5-6 times a day, vomiting after meals 1-2 times a week, tearfulness, sleep disturbances.

Medical history. Stool is liquid, abundant up to 5-6 times a day, observed from the 6th month of life, after the introduction of complementary foods. Complaints of periodic vomiting, loss of appetite, flatulence, present since 7 months. Faecal analysis

for intestinal group microbes is repeatedly negative.

She was born in the third pregnancy without complications; third delivery by caesarean section with Apgar score 8/9, birth weight 4000 g, height 55 cm. The girl was breastfed for up to 1 month, then weaned on a special formula. Due to the low income of the family, the baby was also fed with semolina and oatmeal porridge. The mother periodically offered the child bread and biscuits. Development is delayed: does not sit or stand. Babbles - on time.

Allergy anamnesis: diaper dermatitis at age of 3 months.

Family anamnesis: child's mother periodically complains of abdominal pain and loose stool.

The child's general condition is moderate. Delayed physical development. The child's weight on admission was 6,600 g, height 72 cm. Deficit in body weight - 25.5%. Muscular hypotonia of limbs and anterior abdominal wall, protruding forehead and parietal humps. Skin was pale, clear, dry. The subcutaneous fat layer is thin on the abdomen, trunk and limbs. Abdomen is soft, moderately distended, painless, liver is palpable +2.5 cm below the costal arch. Stool is type 7 on the Bristol chart.

The differential diagnosis included celiac disease, gluten intolerance and wheat allergy. Examinations:
- CBC: iron deficiency anaemia.
- Urinalysis, stool test, urine amylase test – normal findings.
- D(25(OH)) – 15 ng/ml (reference value – 30-70 ng/ml).
- IgA in blood serum - 0.4 g/l. (reference value – 0.02-0.83 g/l).
- IgG autoantibodies to gliadin 35.2 IU/ml (up to 1 year up to 3 IU/ml).
- IgA autoantibodies to tTG less than 1 IU/ml (reference value – less than 20 IU/ml).
- IgG autoantibodies to tTG 14.5 IU/ml (reference value – less than 20 IU/ml).
- IgA antibodies to endomysium – titre 1:5 (reference value – less 1:10 – negative).
- Abdominal ultrasound: liver size +1 cm.
- - Endoscopy: erythematous duodenopathy, mild, with elements of lymphofollicular hyperplasia of the duodenal mucosa. Pathomorphological conclusion: normal histostructure of the mucosa.

Diagnosis: Gluten intolerance. Vitamin D-deficient rickets. Moderate protein-energy deficiency.

The child was prescribed a gluten-free diet and the nutritional status was corrected (including vitamin D). Positive dynamics of intestinal symptoms, body weight and psychomotor development were noted within 6 months.

Clinical case No.2

Girl P., 1 year 4 months old, parents complain about the baby's lethargy, anxiety, abdominal distension, weight loss, defecation disorders (alternation of small amounts of stool with periodic watery stool, up to 5-6 times a day).

The child was born from the first pregnancy against the background of anaemia and mild pre-eclampsia, Apgar score 7/8, body weight 3000 g, body length 50 cm.

The girl was breastfed up to 3 months, then due to hypogalactia of the mother she was transferred to artificial feeding with adapted milk formula. This resulted in hyperemia and dry skin. Cereals (including oatmeal) were introduced at 6 months. Stool was mushy, 1-2 times a day.

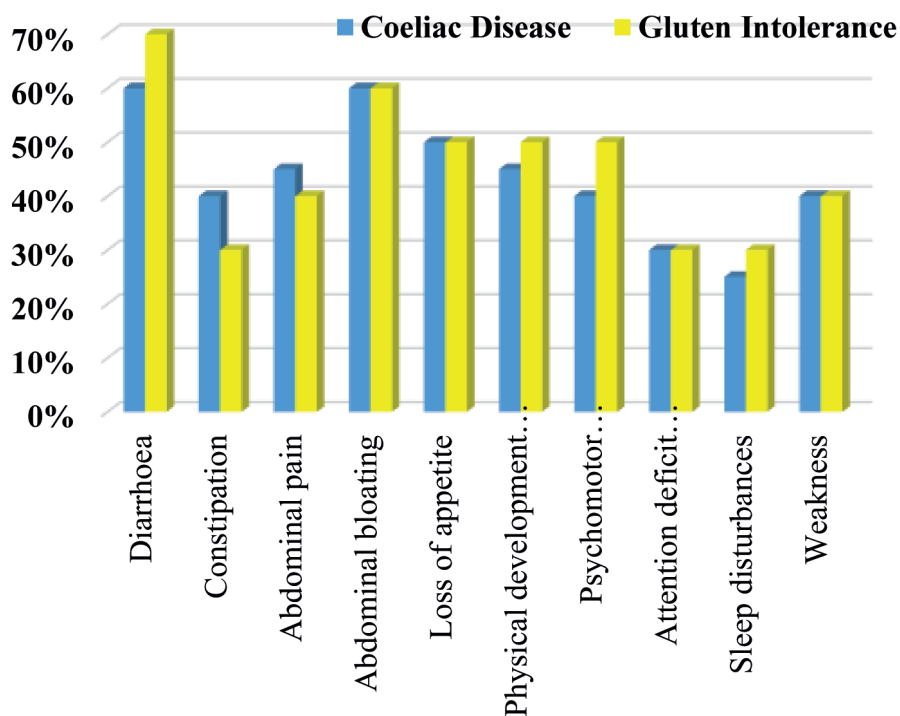The girl has been growing and developing normally by the age of one year.

Fig. 1 Intestinal and extra-intestinal manifestations in children with celiac disease and gluten intolerance

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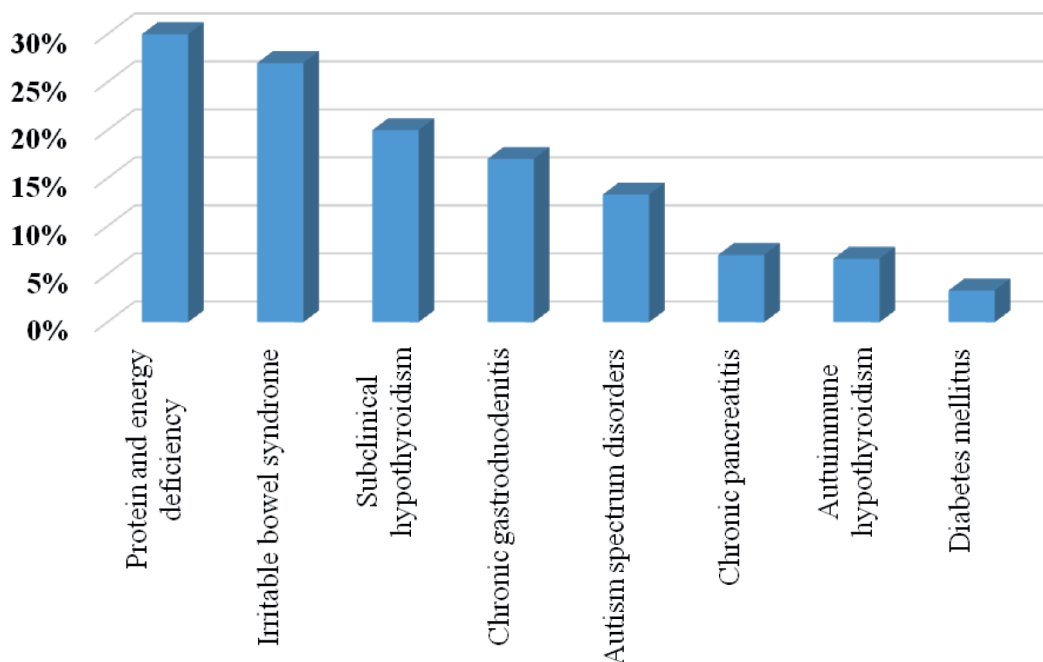
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Fig. 2. Associated pathology in children with gluten-dependent diseases

At the age of 1 year and 2 months, vomiting occurred up to 3 times a day, loose stools - up to 3 times a day, no fever. Examined by a paediatrician: preliminary diagnosis - teething. In 5 days motor activity decreased, abdominal distension appeared, stool became more frequent up to 5-6 times a day, liquid. Despite good appetite, the child began to lose weight and was admitted to the paediatric infectious diseases department with a diagnosis of acute enterocolitis. No positive dynamics on treatment, so the girl was transferred to the gastroenterology department because of suspicion of gluten enteropathy.

The state on admission was severe because of the asthenic and dyspeptic syndrome. Body weight deficit was about 12% (weight on admission - 9,640 g, correct weight - 11,000 g). Skin: pale, greyish, dry. The subcutaneous fat layer was slightly thinned. Muscle tone was diffusely reduced. Auscultation of the lungs: childish breathing, no wheezing. Heart sounds were rhythmic, muffled. The abdomen was enlarged, distended. There was a rumbling sound along the colon. Symptoms of peritoneal irritation were negative. Liver: +3 cm below the costal arch. Stool: once a day with a small amount of faeces. Urine: transparent, pale yellow.

Examinations:

- CBC: mild hypochromic anaemia (haemoglobin – 9.0 g/ml, microcytosis, anisocytosis, colour index – 0.78).

- Biochemical blood test: decrease of total protein, hypalbuminaemia, iron – 6.2 nmol/l (reference value – 8.8-27 nmol/l), ferritin – 4.6 ng/ml (reference value – 7-140 ng / ml).

- Urinalysis – normal findings.

- Stool test: steatorrhea, amylorrhoea, moderate amount of mucus.

- Faecal bacteriology: moderate growth of E. coli.

- Serum IgA - 0.83 g/l (reference value – 0.2-1 g/l).

- Immunoglobulin IgA to tTG - 220 IU/ml (reference value – less than 20 IU/ml).

- Abdominal ultrasound: diffuse changes in the liver parenchyma; a lot of content in the stomach, increased peristalsis of the lower intestine, liquid content.

- Colon X-ray: shape of the colon is changed; contours of the intestine are even, wall is elastic, no defects, lumen is patent and narrowing after defecation.

- Endoscopy: normal colour of mucosa oesophagus, stomach and duodenum. Cardia is closed. Biopsy was taken. Histological examination of the duodenum mucous membrane: flattening of the villi, oedema and moderate lymphoplasmacytic infiltration of the stroma.

- Endoscopic rectosigmoidoscopy: catarrhal proctosigmoiditis.

Diagnosis: Celiac disease, typical form. Megacolon. Mild iron deficiency anaemia. Protein-energy deficiency of the 1st degree.

The girl received treatment: therapeutic polymer nutrition (water-based porridges, like buckwheat and corn, were introduced 5 days later); infusion therapy with glucose-saline solutions, antibiotics, vitamins, enzymes, probiotics. During her stay at the hospital, symptoms of intoxication disappeared, appetite became normal, stool – regular, digested; she began gaining weight, standing up, and walking.

The child was discharged home with the recommendations: strict gluten-free diet, supplementation of vitamins B1, B6, D.

Discussion

Symptoms of gluten-dependent diseases usually appear in children after ingestion of gluten at the age of 4-24 months [4]. In our study, the mean age at diagnosis of celiac disease was 2.8±1.3 years. Major gastrointestinal symptoms such as diarrhoea and abdominal distension are observed in 50% of

patients with gluten-dependent diseases [15, 16]. In our study, these symptoms were found in 60% of the children.

Extra-intestinal manifestations are observed in 60% of children with gluten-dependent diseases, and physical developmental delay is the most common problem [17]. According to the authors, up to 47% of children with gluten-dependent diseases have physical developmental delay, which is similar to the results of our study [15, 18, 21].

Iron deficiency anaemia is present in 40% of children with gluten-dependent disorders [18, 20]. In our study, 60% of children with celiac disease and 40% of children with gluten intolerance had iron deficiency anaemia. According to the literature, extraintestinal symptoms predominate in adult patients with gluten intolerance [14]. The results of our study show that there are no significant differences in the clinical manifestations of celiac disease and gluten intolerance. According to some authors, the prevalence of celiac disease in patients with autoimmune pathology is 3.0%-4.8% [15, 21]. In our study, 6.6% of the children had autoimmune thyroiditis. Other authors have found that 10-30% of children with gluten-dependent diseases have a 25-OH-D3 deficiency [22]. We found that 40% of children with celiac disease and 30% of children with gluten intolerance had 25-OH-D3 deficiency.

The 2020 ESPGHAN guidelines report: The combination of tTG-IgA and total IgA test results is more accurate than other test combinations as an initial investigation in suspected gluten-dependent diseases. In our study, 95% of children with celiac disease were positive for tTG-IgA, while all children with gluten intolerance were negative. This is important for differential diagnosis [6,8].

There is also evidence in the scientific literature that celiac disease is characterised by autoimmune lesions of the small intestine with development of mucosal atrophy, and that only clinical symptoms without structural damage to the small intestinal mucosa are typical of gluten intolerance [23]. In our study, different stages of atrophy of the small intestinal mucosa according to the Marsh-Oberhuber classification were found in all children with celiac disease, and no atrophic changes were found in children with gluten intolerance.

Currently, the only effective treatment for gluten-dependent disorders is a gluten-free diet [24, 25]. Children in our study with a confirmed diagnosis were placed on a gluten-free diet. Improvement in clinical symptoms was seen after 4-6 weeks.

Conclusion

The results of our study indicate that there are no significant differences in the clinical manifestations of celiac disease and gluten intolerance. Gluten intolerance is diagnosed after exclusion of autoimmune nosology in the family history; absence of autoantibodies to tTG, endomysium and deaminated gliadin peptides determined on a gluten-containing diet; absence of specific IgE to wheat; without total IgA deficiency. An important step is the morphological analysis of biopsies of the small intestinal mucosa. Different stages of mucosal atrophy according to the Marsh-Oberhuber classification are characteristic of celiac disease, whereas they are not typical of gluten intolerance, but initial changes in the small intestinal mucosa can be detected: a slight increase in intraepithelial lymphocytes. Clear algorithms proposed by ESPHGAN and the World Gastroenterological Organisation will help in the differential diagnosis of gluten-dependent diseases. In children with unexplained chronic diarrhoea, delayed physical development, delayed puberty, nausea, vomiting, abdominal pain and bloating, chronic constipation, iron deficiency anaemia and elevated liver enzymes, gluten-related diseases should be excluded. Cases have shown significant improvement in children on a gluten-free diet, despite delayed physical development, impaired protein-energy metabolism and poor absorption of vitamins and minerals. Early diagnosis and treatment of coeliac disease prevents the development of serious complications and the manifestation of autoimmune diseases.

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References:

1. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol [Internet]. 2018[cited 2023 May 28];16(6):823-36. e2. Available from: https://www.cghjournal.org/article/S1542-3565(17)30783-8/fulltext doi: 10.1016/j.cgh.2017.06.037

2. Myléus A, Reilly NR, Green PHR. Rate, Risk Factors, and Outcomes of Nonadherence in Pediatric Patients With Celiac Disease: A Systematic Review. Clin Gastroenterol Hepatol. 2020;18(3):562-73. doi: 10.1016/j.cgh.2019.05.046

3. Catassi GN, Pulvirenti A, Monachesi C, Catassi C, Lionetti E. Diagnostic Accuracy of IgA Anti-Transglutaminase and IgG Anti-Deamidated Gliadin for Diagnosis of Celiac Disease in Children under Two Years of Age: A Systematic Review and Meta-Analysis. Nutrients [Internet]. 2021[cited 2023 May 28];14(1):7. Available from: https://www.mdpi.com/2072-6643/14/1/7 doi: 10.3390/nu14010007

4. Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr. 2020;70(1):141-56. doi: 10.1097/MPG.0000000000002497

5. Malik Z. Celiac Disease (Gluten Enteropathy). MSD Manual for the Professional, 2021. Available from: https://www.msdmanuals.com/uk/professional/gastrointestinal-disorders/malabsorption-syndromes/celiac-disease

6. European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), 2020. New Guidelines for the Diagnosis of Paediatric Coeliac Disease. Available from: https://www.espghan.org/knowledge-center/publications/Clinical-Advice-Guides/2020_New_Guidelines_for_the_Diagnosis_of_Paediatric_Coeliac_Disease

7. Auricchio R, Mandile R, Del Vecchio MR, Scapaticci S, Galatola M, Maglio M, et al. Progression of Celiac Disease in Children With Antibodies Against Tissue Transglutaminase and Normal Duodenal Architecture. Gastroenterology [Internet]. 2019[cited 2023 May 28];157(2):413-20.e3. Available from: https://www.gastrojournal.org/action/showPdf?pii=S0016-5085%2819%2935671-9 doi: 10.1053/j.gastro.2019.04.004

8. Rubio-Tapia A, Hill ID, Semrad C, Kelly CP, Greer KB, Limketkai BN, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. Am J Gastroenterol. 2023;118(1):59-76. doi: 10.14309/ajg.0000000000002075

9. Wessels M, Dolinsek J, Castillejo G, Donat E, Riznik P, Roca M, et al. Follow-up practices for children and adolescents with celiac disease: results of an international survey. Eur J Pediatr. 2022;181(3):1213-20. doi: 10.1007/s00431-021-04318-2

10. Hill ID, Fasano A, Guandalini S, Hoffenberg E, Levy J, Reilly N, et al. NASPGHAN Clinical Report on the Diagnosis and Treatment of Gluten-related Disorders. J Pediatr Gastroenterol Nutr. 2016;63(1):156-65. doi: 10.1097/MPG.0000000000001216

11. Valitutti F, Trovato CM, Montuori M, Cucchiara S. Pediatric Celiac Disease: Follow-Up in the Spotlight. Adv Nutr. 2017;8(2):356-61. doi: 10.3945/an.116.013292

12. Francavilla R, Cristofori F, Verzillo L, Gentile A, Castellaneta S, Polloni C, et al. Randomized Double-Blind Placebo-Controlled Crossover Trial for the Diagnosis of Non-Celiac Gluten Sensitivity in Children. Am J Gastroenterol. 2018;113(3):421-30. doi: 10.1038/ajg.2017.483

13. Khan A, Suarez MG, Murray JA. Nonceliac Gluten and Wheat Sensitivity. Clin Gastroenterol Hepatol [Internet]. 2020[cited 2023 May 28];18(9):1913-22.e1. Available from: https://www.cghjournal.org/article/S1542-3565(19)30367-2/fulltext doi: 10.1016/j.cgh.2019.04.009

14. Sapone A, Leffler DA, Mukherjee R. Non-Celiac Gluten Sensitivity – Where are We Now in 2015? Pract Gastroenterol. 2015;143:40-48.

15. Sahin Y. Clinical evaluation of children with celiac disease: a single-center experience. Arch Clin Gastroenterol [Internet]. 2020[cited 2023 May 28];6:026-030. Available from: https://www.peertechzpublications.com/articles/ACG-6-174.php doi: 10.17352/2455-2283.000074

16. Llanos-Chea A, Fasano A. Gluten and Functional Abdominal Pain Disorders in Children. Nutrients [Internet]. 2018[cited 2023 May 28];10(10):1491. Available from: https://www.mdpi.com/2072-6643/10/10/1491 doi: 10.3390/nu10101491

17. Nardecchia S, Auricchio R, Discepolo V, Troncone R. Extra-Intestinal Manifestations of Coeliac Disease in Children: Clinical Features and Mechanisms. Front Pediatr [Internet]. 2019[cited 2023 May 28];7:56. Available from: https://www.frontiersin.org/articles/10.3389/fped.2019.00056/full doi: 10.3389/fped.2019.00056

18. Jericho H, Guandalini S. Extra-Intestinal Manifestation of Celiac Disease in Children. Nutrients [Internet]. 2018[cited 2023 May 28];10(6):755. Available from: https://www.mdpi.com/2072-6643/10/6/755 doi: 10.3390/nu10060755

19. Nardecchia S, Auricchio R, Discepolo V, Troncone R. Extra-Intestinal Manifestations of Coeliac Disease in Children: Clinical Features and Mechanisms. Front Pediatr [Internet]. 2019[cited 2023 May 28];7:56. Available from: https://www.frontiersin.org/articles/10.3389/fped.2019.00056/full doi: 10.3389/fped.2019.00056

20. Nurminen S, Kivelä L, Huhtala H, Kaukinen K, Kurppa K. Extraintestinal manifestations were common in children with coeliac disease and were more prevalent in patients with more severe clinical and histological presentation. Acta Paediatr. 2019;108(4):681-7. doi: 10.1111/apa.14324

21. Sahin Y, Evliyaoglu O, Erkan T, Cokugras FC, Ercan O, Kutlu T. The frequency of celiac disease in children with autoimmune thyroiditis. Acta Gastroenterol Belg. 2018;81(1):5-8.

22. Björck S, Brundin C, Karlsson M, Agardh D. Reduced Bone Mineral Density in Children With Screening-detected Celiac Disease. J Pediatr Gastroenterol Nutr. 2017;65(5):526-32. doi: 10.1097/MPG.0000000000001568

23. Rotondi Aufiero V, Fasano A, Mazzarella G. Non-Celiac Gluten Sensitivity: How Its Gut Immune Activation and Potential Dietary Management Differ from Celiac Disease. Mol Nutr Food Res [Internet]. 2018[cited 2023 May 28];62(9):e1700854. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/mnfr.201700854 doi: 10.1002/mnfr.201700854

24. Trovato CM, Montuori M, Valitutti F, Leter B, Cucchiara S, Oliva S. The Challenge of Treatment in Potential Celiac Disease. Gastroenterol Res Pract [Internet]. 2019[cited 2023 May 28];2019:8974751. Available from: https://downloads.hindawi.com/journals/grp/2019/8974751.pdf doi: 10.1155/2019/8974751

25. Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J. 2019;7(5):583-613. doi: 10.1177/2050640619844125

ПРОБЛЕМИ ДИФЕРЕНЦІЙНОЇ ДІАГНОСТИКИ ЦЕЛІАКІЇ ТА НЕПЕРЕНОСИМОСТІ ГЛЮТЕНУ У ДІТЕЙ

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Резюме

Вступ. На сьогодні у клінічній практиці виділяють 3 види «глютенозалежних захворювань»: целіакія, непереносимості глютену без целіакії (НГБЦ) і алергія на злакові, зокрема пшеницю. Целіакія – це хронічне, імунозапальне захворювання, яке виникає у генетично схильних осіб у відповідь на контакт із основним білком злакових – глютеном, і характеризується ураженням слизової оболонки тонкої кишки та призводить до розвитку її атрофії із відповідними клінічними кишковими та позакишковими проявами; лікується за допомогою пожиттєвої безглютенової дієти. НГБЦ – це стан, який характеризується появою симптоматики, подібної до синдрому подразненого кишечника, за декілька годин або днів після споживання глютеновмісних страв. Ці прояви швидко зникають після припинення споживання глютеновмісних продуктів. Причинами НГБЦ є інгібітори амілази, трипсину та фруктани (FODMAPS), які є складовими пшениці та інших глютеновмісних та безглютенових продуктів харчування. У 2020 році з'явилися нові рекомендації Європейського товариства педіатрії, гастроентерології, гепатології та нутриціології (ESPGHAN) для діагностики целіакії у дітей. Діагноз НГБЦ потребує виключення целіакії та алергії на пшеницю.

Метою дослідження було визначити особливості клінічного перебігу целіакії та НГБЦ (проаналізувати кишкові та позакишкові симптоми), серологічні та морфологічні характеристики для диференціальної діагностики та визначення тактики ведення дітей.

Матеріал та методи дослідження. До дослідження було залучено 30 дітей за період 2016-2023 роки, віком від 9 місяців до 11 років; 13 (43,3%) хлопчиків і 17 (56,6%) дівчаток, p=0,1391. Дослідження включало детальне вивчення анамнезу, оцінку об'єктивного огляду дитини, фізичного розвитку. Визначення загального титру антитіл IgA, IgA до тканинної трансглутамінази (tTG-IgA), ендомізію IgA (EMA-IgA), гліадину IgG, антитіл до пшениці IgE, ендоскопію та морфологічне дослідження біоптатів слизової оболонки дванадцятипалої кишки. Використовували описовий аналіз, порівняння двох пропорцій (непараметричні методи для перевірки висунутих у роботі гіпотез: логістична регресія з використанням показника відносного ризику (RR) і 95% довірчого інтервалу (CI). Різницю параметрів вважали статистично значущою при p<0,05.

Дослідження погоджено Комісією з питань біомедичної етики щодо дотримання морально-правових правил проведення медичних наукових досліджень Харківського національного медичного університету. Встановлено, що дослідження не суперечать основним біоетичним нормам і відповідають основним положенням GCP (1996), Конвенції Ради Європи з прав людини та біомедицини (04.04.1997), Гельсінської декларації. Всесвітньої медичної асоціації з етичних засад дослідження за участю людини (1964-2008) та наказу МОЗ України №690 від 23.09.2009 (зі змінами, внесеними згідно з наказом МОЗ України № 523 від 12.07.2012). Обидва батьки пацієнтів були поінформовані про мету й обсяг дослідницьких процедур і підписали інформовану письмову згоду на участь їхніх дітей у даному дослідженні.

Статистичний аналіз було проведено за допомогою програм Statistica 7.0 StatSoft Inc.1984-2004, (Serial Number 12255555555, USA) and MedCalc version 14.8-© 1993-2014 MedCalc Software bvba (Acacialaan 22 B-8400 Ostend, Belgium). Процедури, логіка та інтерпретація одержаних статистичних параметрів математично-статистичного аналізу базувалися на загальноприйнятих положеннях медичної та біологічної статистики. Використовували описовий аналіз, порівняння двох пропорцій. Використовували непараметричні методи для перевірки висунутих у роботі гіпотез: логістична регресія з використанням показника відносного ризику (RR) і 95% довірчого інтервалу (CI). Різницю параметрів вважали статистично значущою при p<0,05. У процесі дослідження пацієнтів було розподілено на дві групи за діагнозом: целіакія та НГБЦ.

Представлена стаття є фрагментом науково-дослідної роботи кафедри педіатрії №1 та неонатології Харківського національного медичного університету на тему: «Медико-соціальні аспекти адаптації дітей із соматичною патологією в сучасних умовах» (номер державної реєстрації 0120U102471).

Результати дослідження.

У 66,6% дітей із загальної когорти було встановлено діагноз целіакія, а у 33,3% дітей – НГБЦ, p=0,0053. Середній вік дітей із целіакією – 8,4±1,0 рік. Розподіл за статтю серед дітей з целіакією - 50,0% хлопчиків, 50,0% дівчаток, p=1,0000. Середній вік дітей з НГБЦ – 9,1±1,0 рік. Розподіл за статтю серед дітей з НГБЦ - 70,0% хлопчиків і 30,0% дівчаток, p=0,0001. У 65,0% дітей із целіакією діагноз встановлюється на більш ранньому етапі, ніж у дітей із НГБЦ, p=0,0350. Обтяження сімейного анамнезу автоімунною патологією спостерігалось у 40% дітей з целіакією. Усі хворі на целіакію були серопозитивними за серологічними біомаркерами. У 95,0% дітей з целіакією визначались IgA до тканинної трансглутамінази tTG-IgA (RR=20,4; 95% CI 1,4–307,2; p=0,0292).

У 18/30 дітей із загальної когорти було виявлено діарею та болі в животі (RR=0,8; 95% CI 0,4–1,4; p=0,5050), у 17/30 дітей – зниження апетиту (RR=0,7; 95% CI 0,4–1,3; p=0,2695), у 15/30 дітей – закреп і погану прибавку маси тіла (RR=0,7; 95% CI 0,3–1,5; p=0,4209), у 14/30 дітей – затримку фізичного розвитку і слабкість (RR=0,9; 95% CI 0,4–1,9; p=0,7929). Синдром гіперактивності та дефіциту уваги, порушення нічного сну мала третина обстежених дітей. У всіх дітей із целіакією було виявлено різні стадії атрофії слизової оболонки тонкої кишки за класифікацією Marsh-Oberhuber. У дітей із НГБЦ не виявлено атрофічних змін слизової оболонки тонкої кишки (ворсинки та крипти нормальної будови), однак у 60% цих пацієнтів виявлені інфільтративні зміни (збільшення інтраепітеліальних лімфоцитів).

Висновки. Під час проведення порівняльного аналізу достовірних відмінностей між клінічними проявами целіакії та НГБЦ не знайдено. У сімейному анамнезі дітей із НГБЦ автоімунна патологія не виявлена, тоді як у 40% пацієнтів із целіакією він був обтяжений. НГБЦ діагностують після виключення в родинному анамнезі автоімунної нозології; відсутності автоантитіл до тканьової трансглутамінази та дезамінованим пептидам гліадину, ендомізіальних автоантитіл, які визначаються на тлі глютен-вмісної дієти, а також відсутності специфічних IgE до пшениці. У всіх дітей із целіакією виявлені різні стадії атрофії слизової оболонки тонкої кишки за класифікацією Marsh-Oberhuber, а у дітей із НГБЦ атрофічних змін не знайдено, однак у 60% пацієнтів з НГБЦ виявлені інфільтративні зміни слизової оболонки тонкої кишки.

Ключові слова: целіакія; непереносимість глютену без целіакії; безглютенова дієта; діти.

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