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DESTRUCTIVE GASTRODUODENAL PATHOLOGY AS A MASK OF DEBUT OF ATYPICAL FORMS OF CELIAC DISEASE IN CHILDREN

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Theoretical data on the present-day diagnostic algorithm for celiac disease (CD) in children have been presented. The clinical case of CD debut with destructive gastroduodenal zone pathology (GDZ) has been described. This clinical case accentuates the need for special caution of physicians from various specialties concerning CD, the course of which may be masked under various diseases.
Keywords: celiac, gastroduodenal pathology in children.

Most often the differential diagnosis for the diseases of the upper gastrointestinal tract is connected with distinguishing of organic (gastritis, peptic ulcer disease) and functional (functional, non-ulcer dyspepsia) pathology [4,10] and also of associated diseases (GERB, cholepathy). Helicobacter-negative forms of destructive pathology of GDZ require a careful differential diagnosis not only in terms of finding of other infectious factors (Candida albicans, herpes virus), but also excluding diseases such as Crohn's disease and CD [2,4,9].

CD has been considered until recently to be a rare disease with the frequency of 1:5,000–1:10,000. Implementation in practice of highly advanced diagnostic methods has proved the opposite: CD (other names — celiac enteropathy, gluten-sensitive enteropathy, non-tropical sprue, Herter's infantilism) is one of the most common genetically determined diseases, the average frequency of which in the population is 1:100–1:200 [14]. However, despite significant advances in the diagnosis of this the theory of «celiac iceberg» remains urgent, the visible part of which is explicit (diagnosed) cases of CD, and much greater (underwater) part reflects the latent and hidden forms. According to different authors, the ratio of undiagnosed cases of CD to diagnosed ones makes from 5:1 to 30:1. [11]. There is no official statistics about Ukraine. Today there are about 600 patients (association members of patients with CD), which corresponds to the average frequency in the population 0.001:100. Consequently, the ratio of diagnosed cases of CD to the undiagnosed ones in Ukraine is 1:770. Genealogical studies have revealed a high degree of risk of CD among the first degree relatives (1:20), somewhat lower — for the second (1:39) and third (1:56) degrees of affinity [6]. Among the patients with diabetes CD can be diagnosed in 20%. The disease is more common for women than men.

The disease is associated with HLA-class II antigens, including HLA-DQ2 and HLA-DQ8. Individual alleles have proven to have influence on the gravity of CD course [7]. The role of HLA-molecules is the presentation of antigen peptides of graminoids with T-lymphocytes. The disease development includes four phases:

- Gluten (aggregate of graminoid proteins) to form poorly digested fragments — polypeptides.
- Fragments of gluten are modified under the influence of endogenous enzymes of mucus membrane (MM), particularly under the impact of tissue transglutaminase 2 (tTG2) there occurs deamination of glutamine to form glutamic acid.
- Altered gluten fragments bind to molecules HLA DQ2 and DQ8, patients with CD have them.
- Complex of molecules HLA DQ + gluten peptides are identified by T-lymphocytes of mucus membrane (MM) (gluten-specific lymphocytes, healthy people don't have them), which are activated and induce damage.

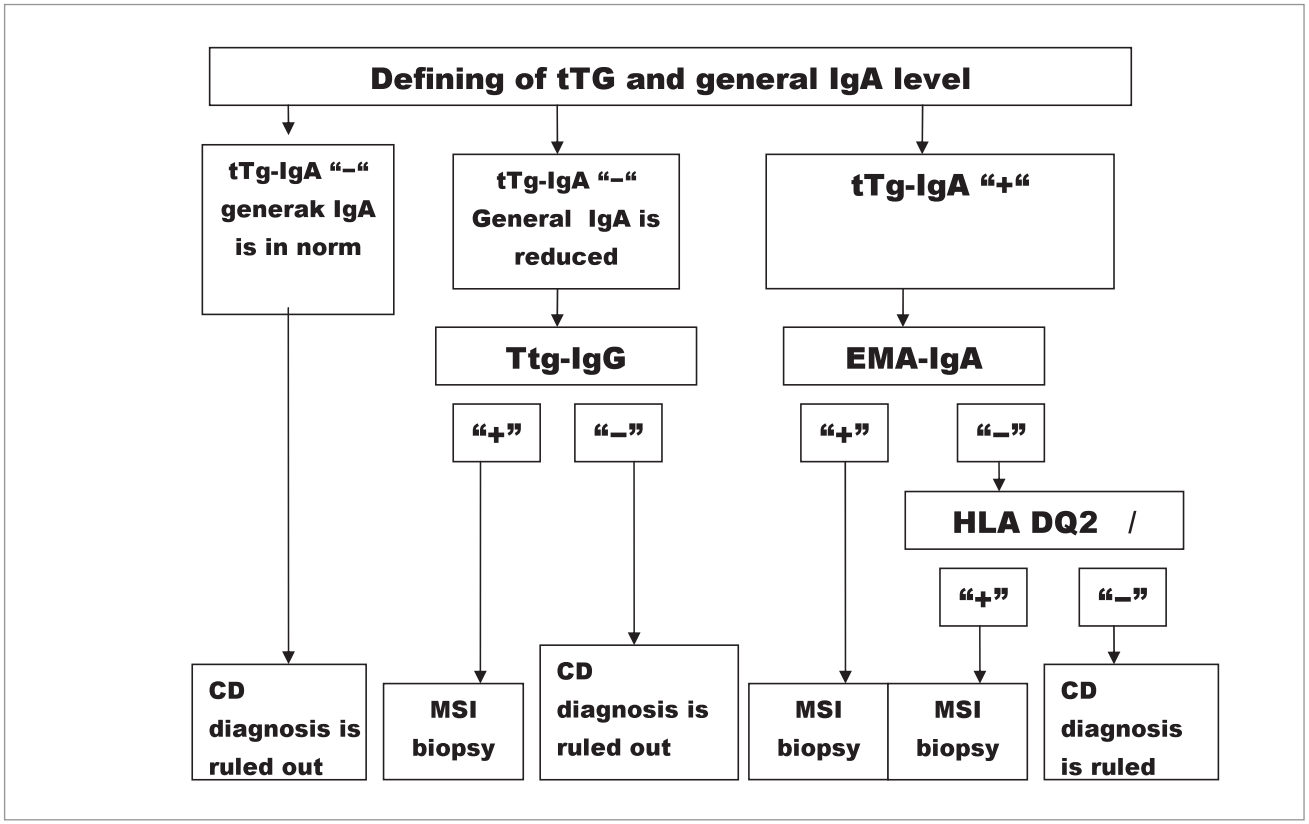

Fig. 1. Algorithm for the celiac disease diagnosis (according to C. Catassi, A. Fasano, 2008)

Thus, a complex immune response, that develops only in patients with CD, gives rise to the disease. Causes of this reaction are still unknown.

According to Z. Kuloglu et al. (2009) [8], approximately 60% of CD in children have a typical course, 40% — the atypical and asymptomatic ones. In typical cases CD is manifested with clinical signs of malabsorption syndrome with fermentative dyspepsia, steatorrhea, weight loss appearing several months after the child's contact with gluten (after the introduction of biekost). Atypical forms usually appear later and begin with nonspecific signs such as lethargy, irritability, unstable «dull» stomach pain, mostly in the periumbilical area, resistant anemia.

Strategy of CD diagnosing today is based not only on clinical presentation, determining of titers of antibodies to tissue transglutaminase and endomysial antibodies, morphological study of the mucosa of the small intestine (Fig. 1). To confirm or to rule out the diagnosis it is necessary to identify the alleles of gene

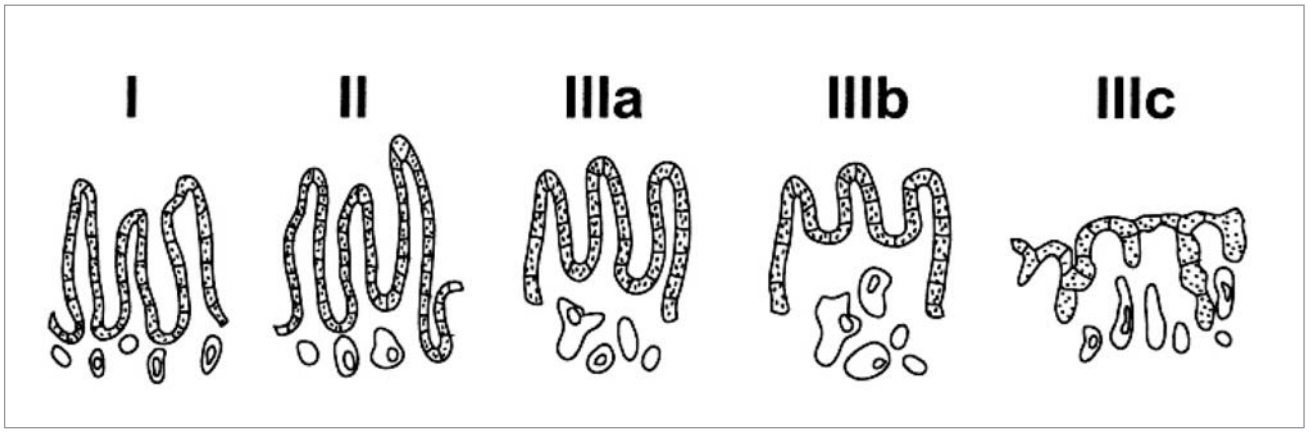

Fig. 2. Morphological diagnosis of celiac disease (in accordance with the classification of M. Marsh in the modification of G. Oberhuber)

HLA DQ2 and HLA DQ8, to have clinical and geneal-ogical study involving relatives and second-degree relatives.

Antigliadin antibodies (AGA) for the diagnosis of CD are not used because of the relatively low sensitivity and specificity. Antibodies to gliadin of IgA class (sensitivity is 66–90%, specificity is 80–100%) should be defined for monitoring of the disease dynamics on the background of gluten-free diet. Antibodies of IgG class (sensitivity 86–94%, specificity 70–87%) should be determined in a selective deficiency of IgA, which among CD patients occurs 10 times more frequently than in the population.

Antibodies to deaminated gliadin peptides (IgA-DGP and IgG-DGP) during the disease development in young children may appear in blood faster than tTG. Sensitivity and specificity approach 100%.

Antibodies to endomysiym (EMA) is a highly specific indicator of antibodies of IgA class (nearly 100% of specificity), sensitivity of which is not sufficient because of possible innate selective deficiency of IgA.

Antibodies to tissue transglutaminase (tTG) — the sensitivity and specificity of the method are close to 100%.

Biopsy of the mucosa of the small intestine (MSI) remains the «gold standard» of CD diagnostics. Biopsy samples are removed during esophagogastroduodenoscopy from the distal dodecadactylon or proximal small intestine. It is important to take several biopsy samples because MM lesion is non-uniform, especially at an early stage.

Morphological diagnosis of CD is done in accordance with the classification of N.M. Marsh (1992) [12] in the modification of G. Oberhuber (1999) [13]. In type 1 changes by Marsh (Fig. 2) the number of intraepithelial lymphocytes (more than 30 lymphocytes per 100 cells) without signs of atrophy SB increase. Type 2 is diagnosed with the ratio of villus: crypt less than 3:1. Type 3 a, b and c reflect the degree of MM atrophy.

Taking into account the significant prevalence of celiac, the availability of reliable diagnostic tests and effective therapies, high probability of delayed diagnosis and irreversible complications, the feasibility of implementing of mass screening programs for this disease has been actively discussed. The main challenge in the developing of such a program is to determine the optimal age for screening, because CD is known to appear at any age. However, nowadays the patients, whose CD exclusion is obligatory, have been clearly defined. Screening of patients is done in the following cases:

- persistent abdominal syndrome;
- anemia;
- osteoporosis;
- autoimmune diseases;
- hepatic dysfunction;
- epilepsy and other neurological disorders;
- Down syndrome, Turner syndrome;
- chronic fatigue syndrome;
- infertility;
- among relatives of patients with CD.

During esophagogastroduodenoscopy the duodenum CD changes may resemble the ones caused by erosive duodenitis (edema, hyperemia, smoothed folds, «mosaic» mucous) [1,5]. According to Y.A. Lysykova et al. (2006) [3], the endoscopic examination in patients with the untreated CD shows signs of duodenitis in 56% of cases, including erosive mucosal changes — 13%. Thus, if there are endoscopic signs of duodenitis in the differential diagnosis the possibility of the gluten enteropathy in a patient should be taken into consideration.

Within five (2006–2010) years under our supervision there were four patients in whom CD debuted under the mask of chronic diseases of GDZ. Here is a clinical case of one of the patients with the confirmed diagnosis of the atypical form of CD, who first was diagnosed with erosive bulbitis.

Mary Y., a girl of 10 years old, was admitted to the department of older childhood of Lviv Regional Children's Clinical Hospital «OHMATDYT» in July, 2009 with the complaints about abdominal pain (epigastric and around the navel areas), frequent headache, bad appetite, emotional lability, constant fatigue. Disorders of intestinal discharge (diarrhea or constipation) were not observed.

The listed above complaints are known from anamnesis to disturb the child from 4 years of age, the child was treated repeatedly about abdominal syndrome with variable outpatient clinic and children's department of the district hospital. The therapy gave a short-term positive effect, but later the complaints renewed. Six months ago, she took patient examination and treatment in the department of older childhood of Lviv Regional Children's Clinical Hospital «OHMATDYT» for chronic gastro-duodenitis, erosive bulbitis. On admission the following symptoms were detected: physical development — reduced (height and weight — by 10–25%), which is regarded as a constitutional feature inherited

through the maternal line, the skin was pale, dry, hair was dry, brittle, prone to loss, mild anemia (Hb — 100 g/l, erythrocytes — $3.12x10^{12}$/l), all biochemical parameters were within age norms; coprogram — neutral fat in large quantities, a moderate amount of undigested fat, mucus, isolated leukocytes; ultrasound of internal organs — liver, gall bladder, lien, kidneys, pancreas were without features, enhanced echo signals from the stomach and duodenum; according to densitometry — osteopenia. Esophagogastroduodenoscopy — gastral MM gastric was hyperemic, moderate swelling, there was a large number of secretory fluid, duodenum MM was edematous, hyperemic with multiple erosions. The morphological study of the gaster showed MM mild inflammation with an insignificant activity of the process, Hp was not found. PH measurement — normal acidity. Echo-encephalography was within normal limits. Received the consultation of neurologist: diagnosed with neurangiosis, asthenic syndrome.

The patient was diagnosed with chronic gastroduodenitis with the preserved acid-forming function, erosive bulbitis.

Assigned treatment: the means antisecretory preparations, antacids, prokinetics, sedative herbs. The state with positive dynamics — cessation of abdominal pain, less frequent headaches, improved performance and appetite. The child continued outpatient treatment, the control examination in 1 month was appointed. Parents didn't come.

However, in 6 months the state of the girl worsened — visible weight loss, renewed abdominal pain, lost appetite, emotional lability was accompanied by the aggressive behavior, especially relative to the younger sister. Parents repeatedly appealed to Lviv Regional Children's Clinical Hospital «OHMATDYT», the child was hospitalized.

From the anamnesis vitae the child is known to be born from pregnancy I, I termbirth. Birth weight was 3500 g, Apgar score was 9–10 points. The girl was breastfed till 1 year and 4 months, the first biekost (milk porridge) was in about 6 months. The physical development of the child corresponded her age till 1 year. In 1 year she weighed 10–11 kg. At the age of three years there was alopecia areata, which was subsequently overgrown. Slight body mass underdevelopment was certified by the district pediatrician at the age of 4 when girl's appetite grew worse, the child became irritable. Thus, a low weight was connected with this and behavioral disorders — with the birth of a second child in the family. The girl didn't suffer from children's infectious diseases, but there were frequent respiratory infections and several cases of stomatitis.

Hereditary history regarding GDZ diseases is not burdened. Paternal grandfather died of intestinal tumors (a detailed diagnosis was not informed by the parents). Maternal aunt had diabetes.

During the repeated admission a significant physical underdevelopment was stated — body weight (20 kg) and height (128 cm) were within 3–10%, the skin was pale (Hb — 90 g/l). The abdomen was slightly swollen, no pain on palpation.

Taking into account the growing gap in physical development, stable anemia, intermittent and partial effect of prescribed therapy, detected changes in Coprogram (expressed steatorrhea, fecal reaction was acidic) as well as hereditary history data (grandfather died of intestinal tumors) the child was supposed to have CD. The blood was taken for antibodies to tissue transglutaminase (IgA, IgG). The result was positive. There were no changes in the esophagus and gaster durin gesophagogastroduodenoscopy, duodenum MM was swollen, «diverse». MM biopsy samples from postbulbar and descending parts of the duodenum were taken. During the morphological study of biopsy samples the increased number of intraepithelial lymphocytes was detected (more than 40 per 100 cells) naps were thickened and flattened, their number was reduced. The number of crypts was moderately increased. Own plate contained the diffuse inflammatory infiltrate, which was dominated by lymphocytes and plasma cells. In addition, there were rare focal lymphocytic infiltrates. Thus, morphological changes corresponded to stage III of MM changes of a small intestine by M. Marsh [12] in G. Oberhuber modification [13].

During immunogenetic study of gene HLA DQA1 alleles the patient was found out to be the carrier of allele DQA1*0501/*0501 (homozygote).

Therefore, the diagnosis of CD was confirmed. The child was assigned a gluten-free diet. During the examination in 6 months child's state was with the marked positive dynamics — weight increased by 3.5 kg. There was no abdominal pain; the headache was less severe, less frequent. The girl became calmer, even-mided, did her homework quicker and got better grades in school. Hemoglobin level increased to 112 g/l without additional prescribing of iron-containing medicines. Control scatological study was a moderate steatorrhea.

The parents were warned of the necessity to examine the first-degree relatives. The parents refused to

undergo the examination, indicating the absence of any clinical symptoms. The younger daughter was examined on the level of antibodies to tissue transglutaminase. The result was negative.

Thus, the child was diagnosed with the atypical form of CD. The atypical symptomatic form of the disease usually makes its debut in the preschool and school age, it is dominated by the extraintestinal symptoms — growth retardation, osteopenia, iron deficiency anemia, arthritis, arthralgia, frequent stomatitis, disorders of the nervous system (ataxia, peripheral neuropathy, myopathy, paresthesia) and psycho-emotional disorders (depression, anxiety). Diagnosis of CD is always difficult, because on the one hand, there are no symptoms that all patients could have, and on the other hand, the various organs and systems clinical manifestations, which complicates their integration into a single diagnosis, conceals the only reason of polymorphic symptoms.

Analyzing the clinical case presented, it should be emphasized that the diagnosis of CD could be ruled out or confirmed as early as at the age of four on the basis of the physical underdevelopment, the presence of abdominal syndrome, anemia and neurological symptoms. Hereditary history could help to diagnose with CD: intestine carcinoma of the grandfather on father's side, associated diseases (diabetes mellitus) on mother's side. This case emphasizes the need for special caution of physicians of various specialties about CD, the course of which may be masked by various diseases. Early CD diagnosis and timely assignment of therapy will help reduce the risk of irreversible complications of CD that can be lethal for a patient.

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