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REVIEW ARTICLE

Celiac disease in children

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Summary

Celiac disease is a multisystemic autoimmune disease induced by gluten in wheat, rye, and barley. It is characterized by polygenic predisposition, high prevalence in members of the Caucasian race (1%), especially in close relatives (5-15%), very heterogeneous expression, and frequent association with other autoimmune diseases (3-10%), as well as selective deficiency of IgA and Down, Turner, and Williams syndromes. The basis of the disease and the key finding in its diagnostics is symptomatic or asymptomatic inflammation of the small intestinal mucosa, which is resolved by a gluten-free diet. Accordingly, the basis of the treatment involves an elimination diet, so the disorder itself, if timely recognized and adequately treated, is characterized by an excellent prognosis.

Keywords: celiac disease, children, clinical forms, diagnostics, therapy

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INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease induced by gluten found in wheat, rye, and barley in genetically predisposed individuals (1, 2, 3). It occurs in all population groups and, most often, in members of the Caucasian race (1:100). (3-6). Like other autoimmune diseases, it is more frequent in females than in males (1.5:1 to 2:1) (7, 8, 9). It is prevalent in first- and second-degree relatives (5-15%) (10). With slightly lower frequency (3-10%), it also occurs in patients with other autoimmune diseases, selective IgA deficiency, and Down, Turner, and Williams syndromes (1, 3, 6, 11-15).

Non-specific inflammation of the small intestinal mucosa resolved on a gluten-free diet represents the main feature of the disease and the basis of its diagnosis (1, 3, 6, 16, 17). In addition to damage of the small intestinal mucosa, which can be symptomatic or asymptomatic, the disease is also characterized by numerous extraintestinal manifestations and, in cases diagnosed too late or treated inconsistently, by potentially severe complications (3, 4, 9, 18-24).

PATHOGENESIS

The pathogenetic basis of CD is a polygenic predisposition and exposure to gluten (3, 25). In addition to gluten, gastrointestinal infections, alterations in the gut microbiota, some medications, and other factors play an important role in the onset of the disease, which explains its incomplete prevalence in monozygotic twins (83-86%) (3, 10, 11, 25, 16). Evidence point to the principal role of polygenic inheritance in the occurrence of the disease, its highly variable frequency in different populations, as well as its high presence in identical twins and first-degree relatives (~10%) (10, 11, 13, 26). The HLA class II genes DQ2 and DQ8 (6p21.32), present in 98-99% of patients, play a central role in hereditary predisposition to the disease (6, 10, 25, 27). HLA DQ2 molecules are registered in 85-95% of patients, and HLA DQ2 in 5-15% of patients (28, 29). However, apart from HLA DQ2 or DQ8 genes and exposure to gluten, the presence of one or more of approximately 40 non-HLA genes that have been verified so far is indispensable for the onset of the disease (3, 11, 13, 25).

The importance of DQ2 and DQ8 glycoproteins present on antigen-presenting cells (dendritic cells and macrophages) in the pathogenesis of CD is reflected in their ability to activate intestinal CD4+ T-cells after binding with deaminated gluten polypeptide hydrolysates (2, 3, 11). The deamidation of gluten hydrolysates, which increases their binding affinity to HLA DQ2 and DQ8 molecules, is performed by tissue transglutaminase (tTG). Proinflammatory cytokines released by activated CD4+ T-cells activate intraepithelial cytotoxic CD8+ T-cells, which lead to enterocyte apoptosis and infiltrative or infiltrative-destructive inflammation of the small intestine mucosa. They also lead to the differentiation of B lymphocytes into plasma cells, as well as to the production of antibodies against gluten peptides and autoantibodies to tTG, endomysium and other body structures (10, 25).

THE ENTEROPATHY

Enteropathy, a structural injury to the small intestine mucosal layer, mainly affects the duodenum and the proximal jejunum, and this process severity progressively decreases towards the ileum (30). Sometimes, however, this mucosal lesion may only affect the duodenal bulb (1, 6, 16). The three primary, distinctive forms of this inflammatory process in the mucosa of the small intestine, defined by modified Marsh criteria, are infiltrative (I), infiltrative-hyperplastic (II), and destructive (III) (31). In the infiltrative form, there is stromal lympho-plasmocytic infiltration, accompanied by an increase in the number of intraepithelial γ/δ lymphocytes. At the same time, alterations in the height of the intestinal villi and crypt depth do not occur. In the second form, in addition to the more pronounced infiltration, hyperplasia of the crypts is observed. In contrast, in the third (destructive) form, the additional, accentuated infiltration and hyperplasia of the crypts, with shortening and/or loss of villi, occurs. According to the degree of mucosal damage, destructive enteropathy is further classified into partial (IIIa), subtotal (IIIb), and total (IIIc) **(Figure 1)**. Apart from this, the fourth form of damage may also occur, and it is characterized by complete atrophy of the villi, but with no crypt hyperplasia and typical signs of mucosal inflammation.

CLINICAL FORMS OF THE DISEASE

Considering the aspect of manifestation, there are two primary clinical forms of CD: symptomatic and asymptomatic (subclinical) (1, 2, 16). Within the framework of symptomatic disease, forms with classical and non-classical clinical presentation are distinguished (1, 2, 16). The characteristics of classical celiac disease are chronic diarrhea, malabsorption, and consequent malnutrition. Extraintestinal manifestations are most conspicuous when it comes to the clinical presentation of the non-classical disease (1, 2, 16, 22, 23). The classical celiac disease form most often occurs in infants and young children. The non-classical disease form occurs in later ages and in adults (11, 16, 23). In the symptomatic form of the disease, the autoantibodies, anti-transglutaminase (AtTG), and anti-endomysial (EMA) antibodies, as well as the HLA DQ2 and DQ8 genotype, are almost regularly registered in addition to the evident enteropathy (1, 2, 12, 27, 29). However, despite the presence of all these indicators,

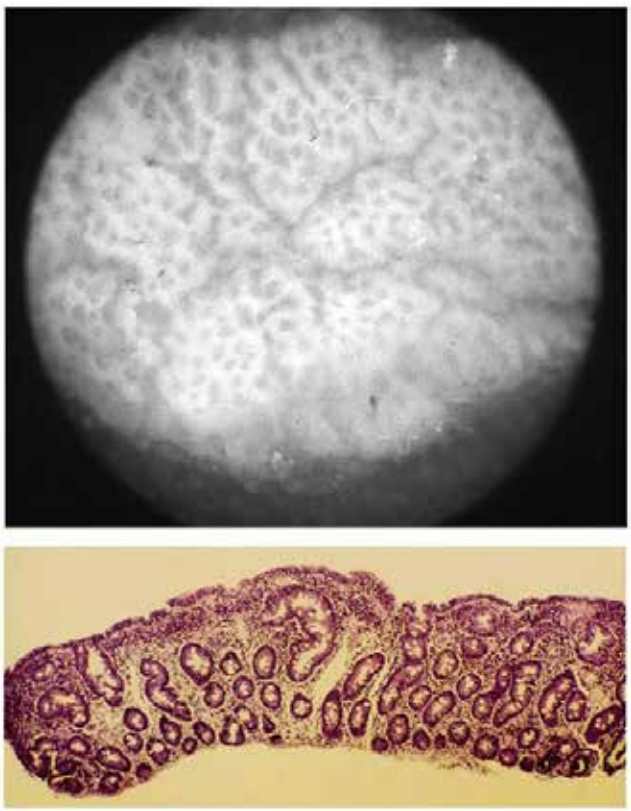

Figure 1. The stereomicroscopic and pathohistological appearance of the mucosa of the small intestine with the most severe degree of damage (Marsh IIIc). The stereomicroscopic image shows the lack of villi with crypt openings, and the pathohistological image shows hyperplasia of the crypts with pronounced lymphoplasmacytic infiltration of the lamina propria. (Original recordings by the authors.)

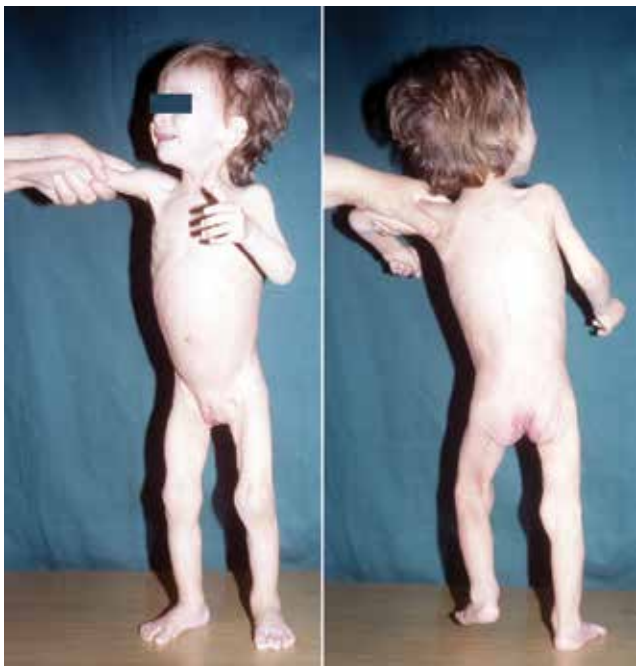

Figure 2. A 20-month-old girl with the classical clinical form of celiac disease. In addition to the typical clinical aspect, there is a noticeable loss of fat and muscle tissue in the gluteal region ("tobacco bag phenomenon") and perianal erythema due to secondary lactose intolerance. (Original recordings by the authors with parental permission.)

in most cases, CD does not manifest itself for a long time, and this form of the disease is called subclinical ("silent celiac disease") (1, 2). In addition, potential CD has an asymptomatic character, which differs from the previous one in the normal appearance of the small intestine mucosa (1, 2, 27). In a significant number of patients with potential CD, enteropathy is also registered later (1).

In children of the youngest age (9-36 months), CD almost regularly occurs in the classical clinical form (9, 16). It is characterized by a relatively short period after the introduction of gluten into the menu, a gradual onset, and a progressive course manifested by chronic diarrhea, anorexia, occasional vomiting, abdominal distension, apathy, and irritability (16). Because of insufficient intake and malabsorption of nutrients, global malnutrition occurs, accompanied by sideropenic anemia, a loss of fat tissue, and reduction of bone and muscle mass **(Figure 2)** (32, 33)**.** In most severe cases, secondary lactose intolerance, isolated hypertransaminasemia ("celiac hepatitis"), and sometimes the appearance of hypoproteinemic edema are registered (20, 33). Within the first 6-9 months upon birth, the disease usually has a rapid and severe clinical course. In rare cases, the so-called "celiac crisis" is characterized by total gastrointestinal insufficiency followed by severe dehydration, metabolic acidosis, meteorism, drastic weight loss, and hypoproteinemic edema (9).

The onset and course of the disease in preschool children are predominantly non-classical (atypical) (16). Compared to an earlier age, gastrointestinal disturbances are less often present or completely absent. Recurrent abdominal pain and constipation, sometimes diarrhea, and often sideropenic anemia, poor appetite, malnutrition, stagnation, stagnation in longitudinal growth, and a change in the child's personality are encountered.

When it comes to symptomatology of the disease in later childhood and adolescence, mono or oligosymptomatic extraintestinal manifestations are dominant (16). In addition to the manifestations seen in preschool age, there are others, such as maturation delay, enamel hypoplasia, recurrent aphthous stomatitis, chronic malaise, dermatitis herpetiformis, osteopenia, arthralgia, myalgia, cerebellar ataxia, polyneuropathy, epilepsy, and others (3, 6, 16, 22, 34).

Although the classical form of the disease is the most often described and best-studied entity, nowadays it is known that it represents only the "tip of the celiac iceberg" and that the largest number of patients, both children and adults, are those with non-classical and subclinical forms of the disease (16)**.**

CELIAC DISEASE AND OTHER DISEASES

Besides the frequently observed presence of celiac disease among patients' close relatives, particularly first-degree relatives, this pathology is commonly associated with

other coexisting autoimmune diseases (3-10%), such as type I diabetes mellitus, thyroiditis, Addison's disease, rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, Sjögren's disease, autoimmune diseases primarily affecting the liver, IgA nephropathy, myasthenia gravis, psoriasis, dilatative cardiomyopathy, and autoimmune pericarditis. (1, 6, 11-15). Approximately the same prevalence of the disease occurs in selective IgA deficiency, as well as in Down, Turner, and Williams syndromes (1, 3, 13).

DIAGNOSIS

The diagnosis of CD is based on an enterobiopsy with pathohistological examination of the mucosa of the small intestine (1, 3, 6, 16, 17). Biopsies are obtained from the duodenum using an upper gastrointestinal endoscopy, whereby 1 or 2 from the bulb and ≥4 from the distal duodenum (1, 3, 16). Such, i.e., multiple enterobiopsies, are necessary because the histological changes may be patchy in distribution and confined to the duodenal bulb. In order to provide adequate samples for pathohistological analysis, the correct orientation of the biopsies is required.

Recommendations of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published in 2012, unlike previous ones, consider that enterobiopsy is not necessary in patients with symptoms and/or signs consistent with CD, and in addition, they have IgA titer antibodies to tissue transglutaminase (AtTG-IgA) ≥10 times above the upper reference value, positive antiendomysial antibodies of the same class (EMA-IgA) and "celiac HLA" (DQ2 and/or DQ8) (1). Clinical recovery of the patient and the disappearance of AtTG are part of the confirmation of the disease, i.e., the justification for the introduction of a gluten-free diet without a previous enterobiopsy. This attitude in the diagnosis of CD is based not only on high sensitivity and specificity of AtTG-IgA as a serological marker of the disease (>95%), but also on the highly significant correlation of their titer with the degree of damage to the mucosa of the small intestine, as well as the almost inevitable correlation (>98%) presence of HLA DQ2 and/or DQ8. An additional difference compared to the previous position is that even in children under two years of age with an exact diagnosis of CD, a gluten provocation test with pathohistological analysis of the small intestine mucosa are not required. However, in patients in whom a gluten-free diet was introduced without a previous enterobiopsy, as well as in cases where the morphological damage of the mucosa was not typical, or the samples were inadequate for a reliable interpretation, the final confirmation or exclusion of CD is based on enterobiopsy and pathohistological findings during the gluten provocation test. Since it can jeopardize the quality of permanent teeth, this procedure is not recommended before the age of six and because of the side effects related to the child's growth and development during puberty.

ESPGHAN, as part of the additional modification of the criteria for the diagnosis of CD, adopted in October 2019 and published in January 2020, does not consider enterobiopsy with pathohistological analysis of the small intestine mucosa samples necessary even in asymptomatic patients with a serum level of AtTG-IgA class ≥10 times above the upper reference level values and positive EMA-IgA (27). Also, bearing in mind the almost absolute association of CD and HLA DQ2 and/or DQ8 in these patients, as well as in those whose diagnosis was established by enterobiopsy, testing in this sense is not necessary. However, in all other cases, the diagnosis of CD requires strict adherence to the 2012 criteria. It is additionally recommended that, as part of the initial serological screening for CD, with prior verification of normal serum IgA for age, AtTG-IgA should be used, and not EMA and antibodies to deamidated gliadin peptide (AtDGP). However, if it is a suspected patient with IgA deficiency, tests based on IgG class antibodies (AtDPG, EMA or AtTG) should be used to this purpose. If there is a discrepancy between the level of AtTG-IgA and the pathohistological findings, it is necessary to re-evaluate the result of the biopsy or consult another pathologist. Patients with elevated serum levels of AtTG-IgA and EMA-IgA in whom normal or minimally damaged small intestine mucosa (Marsh 0/I) was registered require strict monitoring.

Except in the above-mentioned exceptions, serological tests for CD have no diagnostic value (1, 6). Hence, they are primarily used for detection of asymptomatic and non-classical forms of the disease and in the assessment of the consistency of the elimination diet in patients in whom it has been established (1). When interpreting serological screening, it should be kept in mind that it can be positive even without the characteristic damage of the small intestinal mucosa, which is also found in other autoimmune diseases and in other pathological conditions (1). Contrary to this, due to the immunological immaturity of children under two years of age, AtTG may be negative despite evident enteropathy (6, 16). For this reason, when screening children younger than two years of age for CD, the IgA TTG test should be combined with deamidated gliadin peptide (IgA and IgG) (6, 16).

THERAPY

Patients with CD should adhere to a gluten-free diet for life (1, 3, 6, 16, 17). Most of those with a symptomatic form of the disease, especially the classical one, during the initial phase of treatment, require the correction of micronutrient deficits, primarily iron, and folate, and sometimes temporary restriction of lactose (6, 33). In patients with "celiac crisis", in addition to correcting hydro-electrolyte and acid-base imbalance and removing

edema, semi-elemental and additional parenteral nutrition is applied, and exceptionally rarely short-term glucocorticoid therapy (9, 35).

PROGNOSIS

The prognosis of timely recognized and adequately treated CD is excellent (11, 31). Delayed recognition of the disease or non-compliance with the elimination diet, however, can lead to severe consequences, including serious complications, both during growth and development, and those that manifest in adulthood, such as enteropathy-associated T-cell lymphoma, small bowel adenocarcinoma, osteoporosis, infertility, and others (3, 9, 11, 18, 21, 23).

CONCLUSION

Celiac disease denotes a genetically predisposed autoimmune pathology whose onset is triggered and precipitated by the intake of gluten found in wheat, barley, and rye. Most often, it affects Caucasians, it frequently occurs in close relatives, and it should be noted that it is in some cases accompanied by other autoimmune diseases, a selective deficit of IgA antibodies, as well as Down, Turner, and Williams syndromes. The highlight of celiac disease is the non-specific small intestinal mucosal inflammation that completely ceases and is resolved upon introducing a gluten-free diet. Besides enteropathy, which can be either symptomatic or asymptomatic, celiac disease is also characterized by various extraintestinal manifestations. Timely recognition and proper treatment provide excellent prognoses in patients with this condition.

Author contributions

ZL and NR contributed to study design, data analysis and interpretation and they also drafted the manuscript. VR, MM, SD, and BB contributed to data analysis and interpretation, and provided critical review of the intellectual content of the manuscript. PR contributed to data collection, data analysis and interpretation. All the authors approved the final version of the manuscript before submission.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest

None to declare.

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CELIJAČNA BOLEST KOD DECE

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Sažetak

Celijačna bolest je multisistemsko autoimunsko oboljenje indukovano glutenom pšenice, raži i ječma. Karakteriše je poligenska predispozicija, visoka prevalencija kod pripadnika bele populacije (1%), posebno kod bliskih srodnika (5-15%), veoma heterogena ekspresija i česta udruženost sa drugim autoimunskim bolestima (3-10%), kao i selektivnim deficitom IgA i Daunovim, Tarnerovim i Vilijamsovim sindromom. Osnova bolesti i ključni nalaz u njenoj dijagnostici je simptomatsko ili asimptomatsko zapaljenje sluzokože tankog creva koje se povlači na dijeti bez glutena. U skladu s tim, osnovu lečenja čini eliminaciona dijeta, tako da poremećaj, ako se blagovremeno prepozna i adekvatno leči, takođe karakteriše odlična prognoza.

Ključne reči: celijačna bolest, deca, klinički oblici, dijagnostika, terapija

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