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Intolerance of gluten-containing cereals

Интолеранција житарица са глутеном

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Intolerance of gluten-containing cereals

Интолеранција житарица са глутеном

SUMMARY
Intolerance of gluten containing cereals (wheat, rye and barley) is an etiopathogenetically heterogeneous and relatively common problem of modern man. It occurs as an adverse immune-mediated condition in genetically predisposed individuals. According to the pathogenetic mechanism of intolerance to the components of these cereals, it is classified into celiac disease as an autoimmune disease, wheat allergy as an allergic disease, and non-celiac gluten sensitivity as a non-autoimmune and non-allergic disease. Each of these disorders is characterized by specific intestinal and/or extraintestinal manifestations, which resolve on a gluten-free diet. This review article presents the basic characteristics of these disorders in accordance with modern knowledge.
Keywords: gluten-containing cereals; clinical forms of intolerance; celiac disease; diagnostics; nutrition; pediatrics

САЖЕТАК
Интолеранција житарица које садрже глутен (пшеница, раж и јечам) је етиопатогенетски хетероген и релативно чест проблем савременог човека. Јавља се као нежељено имунолошки посредовано стање код генетски предиспонираних особа. Према патогенетском механизму интолеранције компоненти ових житарица, класификује се на целијачну болест као аутоимунску, алергију на пшенично брашно као алергијску и нецелијачну осетљивост на глутен као неаутоимунску и неалергијску болест. Сваки од ових поремећаја карактеришу специфичне интестиналне и/или екстраинтестиналне манифестације, које се повлаче на дијети без глутена. У овом прегледном чланку приказане су основне карактеристике ових поремећаја у складу са савременим сазнањима.
Кључне речи: житарице са глутеном; клинички облици интолеранције; целијачна болест; дијагностика; исхрана; педијатрија

INTRODUCTION

Gluten-containing cereals (wheat, rye and barley) represent an everyday part of the diet of a large part of the human population [1, 2]. They are an important source of polysaccharides, proteins, B vitamins, minerals and a small amount of fat [1, 2]. Wheat flour are extensively included in the menu of man from 10,000 years ago [1, 3]. It is introduced into the infant's diet between 4-12 months after birth [4].

Gluten, a complex storage protein consisting of prolamins and glutenins, makes up about 75–80% of the total flour proteins of wheat, rye and barley [5]. They are characterized by high contents of proline-rich polypeptide residues resistant to effective gastric and pancreatic proteolysis and accordingly high antigenic potential followed by an inadequate immune reaction in genetically predisposed individuals [5-8]. Although both protein components of gluten can cause an inadequate immune reaction, the main causes of intolerance to these grains are prolamins, i.e. wheat gliadin, rye secalin and barley hordein [6]. In addition to gluten, wheat, rye and barley flour contains α-amylase/trypsin inhibitors (ATIs), lectins, non-specific lipid transfer proteins (LTPs) and other proteins, which can also cause adverse immune reactions in predisposed individuals [5, 8].

The spectrum of gluten-related disorders consists of celiac disease, wheat allergy and non-celiac gluten sensitivity [2]. Each of these disorders is characterized by specific intestinal and/or extraintestinal manifestations, which resolve on a gluten-free diet [2]. This review article presents the basic characteristics of these disorders in accordance with modern knowledge.

CELIAC DISEASE

Celiac disease (CD) is a systemic autoimmune disease that occurs in polygenically predisposed individuals on a gluten-containing diet [7, 9, 10]. In members of the white population, it presents with a prevalence of about 1%, while in other population groups it is much rarer or extremely rare [10-13]. It is particularly common in first- and second-degree relatives (5-15%), and somewhat rarer (3-10%) in patients with other autoimmune diseases, selective IgA deficiency and Down, Turner and Williams syndromes [9, 10, 13, 14]. As other autoimmune diseases, it is more common in persons of the female versus male gender (1.5-2:1) [15, 16].

Although the pathogenesis of CD is based on a polygenic predisposition and exposure to gluten, additional factors, such as gastrointestinal infections, alteration of the intestinal microbiota, some medications and others, are also involved in its occurrence, which explains its incomplete prevalence in monozygotic twins (83-86%) [3, 8, 17, 18]. The basic factors in the hereditary predisposition to CD are the HLA genes DQ2 and DQ8 (6p21.32), which are registered in 98 to 99% of patients [8, 13, 19]. HLA DQ2 molecules are found in 85-95% of patients, and HLA DQ8 in 5-15% [20, 21, 22]. However, apart from HLA DQ2 or DQ8 genes, non-HLA genes also have an indispensable presence in the occurrence of the disease [8, 10]. The importance of DQ2 and DQ8 glycoproteins present on antigen-presenting cells (dendritic cells and macrophages) in the pathogenesis of CD lies in their ability to, after binding with deaminated gluten polypeptide hydrolysates, activate intestinal CD4+ T-cells [7, 10]. The deamidation of gluten hydrolysates, which increases their affinity for binding to HLA DQ2 and DQ8 molecules, is catalyzed by tissue transglutaminase (tTG). Activated CD4+ T-cells by releasing proinflammatory cytokines activate intraepithelial cytotoxic CD8+ T-cells, which lead to enterocyte apoptosis and inflammation of the small intestine mucosa, and at the same time, by differentiation of B lymphocytes into plasma cells, the production of antibodies against gluten peptides and autoantibodies to tTG, endomysium and other body structures [8].

Gluten-sensitive enteropathy, i.e. non-specific inflammation of the small intestinal mucosa that resolves on a gluten-free diet, is the main feature of the CD and the basis of its diagnosis [9, 10, 13, 17, 23]. According to the modified Marsh criteria, inflammation of the small intestine mucosa is classified into: infiltrative (I), infiltrative-hyperplastic (II) and destructive (III), whereby the destructive type is additionally differentiated into partial (IIIa), subtotal (IIIb) and total (IIIc) [24]. A fourth type of mucosal damage is also possible, which is characterized by complete atrophy of the villi, but without crypt hyperplasia and typical signs of mucosal inflammation.

Observed from the clinical aspects, CD is differentiated into symptomatic and asymptomatic, while symptomatic, according to the type of manifestation, into classic and non-classic [7, 9, 17]. The classical form of the disease is characterized by chronic diarrhea, anorexia, occasional vomiting and global malnutrition, while in the clinical picture of the non-classical disease extraintestinal manifestations dominate, in a significant number of cases the only [7, 9, 17, 25]. The classic form of the disease is most often seen in infants and young children, and the non-classic in later childhood and in adults [17, 25, 26]. The most frequent symptoms of CD in later childhood and adolescence are sideropenic anemia, poor appetite, malnutrition, short stature, delayed maturation, recurrent abdominal pain, constipation, enamel hypoplasia, recurrent aphthous stomatitis, chronic malaise and change in the personality [10, 13, 17, 25, 27]. The main manifestations of CD in adults are anemia, chronic fatigue, weight loss, recurrent abdominal pain, bloating, flatulence, constipation, mouth ulcer, headaches, depression, and osteopenia or osteoporosis [26, 28]. In addition, women have an increased risk for infertility, miscarriage and early menopause [28]. In about 1-1.5% of total cases of CD, celiac crisis (CC) and refractory CD (RCD) occur [10, 16]. CC is an urgent and potentially fatal complication of untimely recognized CD most often seen in early childhood [16]. It is clinically manifested by deterioration and rapid progression of serious digestive dysfunction followed by profuse watery diarrhea, severe dehydration, metabolic acidosis, meteorism and very pronounced global malnutrition [16]. RCD, which primarily affects adults, is characterized by malabsorption, weight loss, as well as persistent villous atrophy and after 1 year a strict gluten-free diet [7, 13]. There are two subtypes of RCD - type 1, where the phenotype of the intraepithelial lymphocyte population is normal (CD3+CD8+), and type 2, where it is abnormal [10]. RCD, particularly type 2, are highly associated with serious complications, such as ulcerative jejunitis and enteropathy-associated T-cell lymphoma [10, 19]. Although classic type of the CD is the most often described and best studied, today 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 a non-classical and asymptomatic form of the disease [17].

The diagnosis of CD is based on pathohistological examination of the small intestinal mucosa obtained via endoscopic biopsy [9, 10, 13, 17, 23]. Since the histologic changes may be patchy in distribution and confined to the duodenal bulb, 1 or 2 samples should originate from the bulb and ≥4 from the distal duodenum [9, 10, 17]. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), as part of the recommendations published in 2012 considers that enterobiopsy is not necessary in patients with symptoms and/or signs consistent with CD, and in addition, they have an 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) [9]. ESPGHAN, as part of the additional modification of the criteria for the diagnosis of CD, published in January 2020, consider that enterobiopsy is not 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 in a second serum sample (19]. This year's guide related to the diagnosis of CD in children and adults of the American College of Gastroenterology (ACG) do not differ from the latest ESPGHAN recommendations [13]. The American Gastroenterological Association also agrees with the ESPGHAN and ACG guidelines in the diagnosis of CD in children, with the fact that in adults, for purposes of differential diagnosis, upper gastrointestinal endoscopy with duodenal biopsy can also be performed [23]. However, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for the Study of Celiac Disease in their guidelines for the diagnosis of CD include endoscopic enterobiopsy as a mandatory [10, 17]. This attitude is based on the fact that without an endoscopic diagnostic approach, comorbid conditions with CD, such as peptic and eosinophilic esophagitis or Helicobacter pylori gastritis, can be overlooked.

The basis of CD therapy is a gluten-free diet [9, 10, 13, 17, 23]. Most patients with a symptomatic type of the disease, especially with the classical one, during the initial phase of treatment require the correction of micronutrient deficiencies, primarily iron and folate, and sometimes temporary restriction of lactose [13]. Patients with CC, in addition to the correction of hydroelectrolyte and acid-base imbalance and removal of edema, require semi-elemental and/or parenteral nutrition, and sometimes short-term glucocorticoid therapy [10, 16]. RCD therapy also includes parenteral nutrition and immunosuppression with steroids or azathioprine, 6-mercaptopurine, and methotrexate, whereas in the treatment of RCD2 additional medications are

applied, such as cyclosporine, cladribine and fludarabine associated with anti-CD52 monoclonal antibodies (alemtuzumab) [10, 29]. RCD1 usually responds to a gluten-free diet, nutritional support, and immunosuppressive medications, while the therapeutic response in RCD2 is incomplete and, accordingly, prognosis is often poor [13].

The prognosis of timely recognized and consistently treated CD is excellent, while its to late detection or non-compliance with the gluten-free diet, however, can lead to numerous consequences, and sometimes to life-threatening complications [10, 16, 27, 25, 30].

NON-CELIAC GLUTEN SENSITIVITY

Non-celiac gluten sensitivity (NCGS) is a non-allergic and non-autoimmune type of intolerance to wheat, rye and barley flour [31, 32]. It is characterized by a wide range of gastrointestinal and/or extraintestinal manifestations that resolve on a gluten-free diet [10, 31, 32]. Due to the lack of objective diagnostic indicators, the exact frequency of NCIG is not known and according to data from the literature, it occurs in 0.6-6% of members of the general population, whereby six times more often in adult women compared to men [8, 31, 33].

The pathogenesis of NCIG is not clear [2, 8, 10, 31]. It is assumed that the basis of the disorder is an inadequate innate immune reaction to gluten [8, 31, 34, 35]. Activated adaptive immunity is probably involved in the problem [8, 35]. Also, apart from gluten, other components present in wheat, rye and barley flour participate in the pathogenesis of NCGS, such as wheat germ agglutinins, amylase inhibitors/trypsin, and fermentable oligo/di/monosaccharides and polyols [8, 10, 31, 35, 36].

The clinical picture of NCIG is highly variable, both in terms of severity and type of disturbance. It consists of different and most often combined gastrointestinal and/or extraintestinal manifestations [31, 32, 35]. The major gastrointestinal symptoms are episodes of abdominal pain, nausea, heartburn, flatulence, pronounced flatulence, diarrhea and constipation, and extraintestinal symptoms are chronic fatigue, lethargy, anxiety, intermittent headache, depression, skin rash, arthralgia, fibromyalgia and others [8, 31, 33, 35]. Symptoms disappear on a gluten-free diet and appear again after a gluten challenge within a few hours or a couple of days [10, 35].

For now, there are no clearly defined criteria for the diagnosis of NCIG. Studies have shown that half of patients with NCIG have HLA DQ2 and/or DQ8 and positive antigliadin antibodies of the IgG class, but these findings, although almost twice as common as in gluten-tolerant individuals, have no diagnostic value [2, 8, 31, 33]. Also, the microscopic appearance of the mucosa of the small intestine is normal, except for minimal lymphocytic infiltration of the *lamina epithelialis* in a small number of cases [8, 10, 33]. Hence, the basis of the NCIG diagnosis, after excluding celiac disease and wheat flour allergy, is the disappearance or alleviation of symptoms on a gluten-free diet and their reactivation after switching to a standard diet [10, 31, 32, 33]. In cases where the gluten-free diet does not result in the desired effect, when considering the cause of the problems, one should take into account gastrointestinal intolerance of carbohydrates, primarily lactose, idiopathic irritable colon and other conditions with a similar clinical presentation [10, 31, 32].

The basis of the NCIG therapy is the gluten free diet [10, 31, 32, 36]. Unlike CD and WA, fewer patients with NCGS tolerate smaller amounts of gluten containing cereals [10, 35, 37, 38].

WHEAT ALLERGY

Wheat allergy (WA) is the rarest clinical entity within gluten-related disorders. It occurs in 0.2-0.5% of children and in about 0.8% of adults as an immunoglobulin E (IgE) or non-IgE mediated reaction [33, 38, 39]. An important feature of the disorder is the relatively frequent association with other food allergies, such as cow's milk, egg, peanuts, tree nuts, fish and seafood [33, 40].

IgE-mediated WA is characterized by gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), dermal (redness, urticaria**,** angioedema), respiratory (rhinitis, cough, bronchial obstruction), cerebral (headache, dizziness, migraine) and systemic (anaphylaxis) manifestations [31, 33, 38]. Depending on the severity of the reaction, it can be mild to life-threatening, such as anaphylaxis. Adverse reactions are of a rapid type, ie. occurs within 2 hours after exposure to gluten-containing cereals, usually after a few minutes [38]. The reaction is a consequence of T helper type 2 activation and IgE production by B and T cells [38]. The diagnosis is based on the connection between the mentioned clinical manifestations and wheat ingestion, as well as positive in vivo (skin prick tests) and/or in vitro (specific serum IgE) tests [39]. Therapy

involves a strict diet without gluten-containing cereals. In severe allergic reactions, it is necessary to use antihistamines, and in anaphylaxis epinephrine, inhalation beta2-adrenergic agonists, glucocorticoids and other measures [41].

Non-IgE-mediated wheat allergy (delayed onset wheat allergy) represents the pathogenetic basis of eosinophilic esophagitis (EoE) and gastritis (EoG), as well as food protein-induced enteropathy (FPE), food protein-induced allergic proctocolitis (FPIAP) and food protein-induced enterocolitis syndrome (FPIES), which occur in infants and young children [33, 38, 42, 43]. As a consequence of eosinophilic inflammation, symptoms related to EoE are dysphagia, chest pain, regurgitation and food impaction, and for EoG loss of appetite, nausea, vomiting, abdominal pain and sometimes diarrhea [33, 39, 40, 44]. Unlike IgE mediated WA, the etiopathogenesis of these disorders is based on the stimulation of innate immunity through alteration of the mucosal barrier inducing the activation of IL-C2 cells that produce IL-13 and IL-5 responsible for eosinophil recruitment [39, 44]. The diagnosis is confirmed by pathohistological verification of eosinophilic inflammation in biopsies of affected organs [33, 39, 40]. Treatment for EoE and EoG includes proton pump inhibitors (PPI) therapy, corticosteroids, and elimination diets [40, 45]. Esophageal dilation is indicated for treatment of esophageal strictures and fibrostenotic changes [40, 45]. FPE is manifested by chronic malabsorptive diarrhea, intermittent vomiting and failure to thrive, FPIAP with visible specks or streaks of blood mixed with mucous in the stool or mild mucous-bloody prolonged diarrhea, and FPIES with repeated vomiting, profuse diarrhea and severe dehydration [38, 42, 43]. The pathogenesis of these clinical entities is not sufficiently clear, but it is considered that cellular immunity is responsible for driving the allergic inflammatory response [43, 46]. The diagnosis FPIAP and FPIES, with the exclusion of other diseases with a similar clinical picture, remains, for the most part, a clinical one, with the exception of FPE, in which histological confirmation is usually required [43]. In addition to a strict elimination diet, FPE requires the correction of a nutritional deficit, and FPIES the normalization of hydroelectrolyte and acid-base status.

IgE-mediated WA that occurs during early childhood usually disappears with age, while disorders that continue from childhood into adulthood or are adult-onset usually remain permanent [42]. EoE and EoG are usually lifelong disorders, while FPE and FPIAP disappear by the age of 1–2 years, and FPIES by 3–5 years [42, 43].

CONCLUSION

Intolerance of gluten-containing cereals consists of three different immune mediated disorders: CD as an autoimmune, WA as an allergic and NCGS as a non-autoimmune or allergic. After lactose intolerance, it is the most common food-related disorder. This fact should not be surprising, because gluten-containing cereals, as well as animal milk, viewed from the aspect of evolution, have relatively recently become a daily ingredient in the diet of the majority of the human population. They are characterized by highly variable and largely non-specific gastrointestinal and extraintestinal symptomatology, and accordingly the necessity of a subtle diagnostic approach. CD is a permanent disorder, while WA is in a high percentage, especially if it occurs in early childhood, of a transient nature. Also, NCGS can be a transient disorder. The basis of the treatment of all three disorders is a gluten-free diet, with the fact that in NCGS, unlike CD and WA, it does not have to be strict.

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