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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Gluten-related disorders

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SUMMARY
Gluten-related disorders are a heterogeneous group of clinical entities caused by intolerance to wheat, rye, and barley flour components. They occur in 3–5% of genetically predisposed persons and, based on pathogenic and clinical features, are classified into celiac disease, non-celiac gluten sensitivity, and wheat allergy. There are also specific entities such as dermatitis herpetiformis or gluten ataxia, which can occur either within the celiac disease or independently. This article based on the current knowledge shows the basic details of the pathogenesis, clinical expression, diagnosis, and treatment of these disorders.
Keywords: celiac disease; wheat allergy; non-celiac gluten sensitivity; gluten ataxia; dermatitis herpetiformis

INTRODUCTION

Gluten-related disorders (GRDs) cover a group of heterogeneous immune-mediated clinical conditions triggered by the ingestion of wheat, rye, and barley flour [1, 2, 3]. GRDs are in second place among the most frequent food intolerances. They affect about 3–5% of the genetically predisposed human population [4–7]. Classification of GRDs based on variations in pathogenesis and clinical expression identifies celiac disease, non-celiac gluten sensitivity, and wheat allergy [1–4, 8]. As a specific manifestation of the celiac disease or specific clinical entities within the GRDs, gluten ataxia and dermatitis herpetiformis are separated [1, 8–13]. Underlying the pathogenesis of the celiac disease, dermatitis herpetiformis, and gluten ataxia is the immune system's response to gluten intake, IgE-mediated and/or non-IgE-mediated immune response in wheat allergy, and stimulation of the innate immunity with direct cytotoxic effects of gluten and some non-immunological mechanisms in non-celiac gluten sensitivity [1–4, 8, 14]. The basis of the treatment of GRDs is a gluten-free diet [1–4, 8, 15].

CELIAC DISEASE

Celiac disease (CD) is a lifelong systemic autoimmune disorder induced by gliadin and related prolamins of wheat, rye, and barley [1, 16, 17]. Prevalence is about 1% of the general population of European, North African, Indian, and Middle Eastern origin with appropriate genetic foundation [18]. The frequency of CD is more common among close relatives of the diseased, especially those of the first line (~10%) and in patients with other autoimmune diseases (3–10%), such as diabetes mellitus type I, autoimmune thyroiditis, Sjögren's syndrome, Addison's disease, autoimmune liver diseases, juvenile idiopathic arthritis, myasthenia gravis, systemic lupus erythematosus, psoriasis, dilated cardiomyopathy, and others [4, 19]. Multiple-major prevalence of the CD is also recorded in the IgA selective deficit, as well as in Down, Turner, and Williams syndrome [20, 21].

Gluten-sensitive enteropathy is one of the most common findings in patients with CD. This type of enteropathy is nonspecific, affects the small intestine and recedes after switching to a gluten-free diet. Enteropathy in patients with CD can be symptomatic and asymptomatic, and various extraintestinal manifestations and complications are possible [16, 17, 22].

There is no doubt that there is a significant influence of genetic factors in the appearance of CD and its hereditary nature. HLA class II genes have the central role, but it is almost certain that there is influence of other gene loci as well [1, 23]. HLA DQ2 haplotype is identified in about 90% and HLA DQ8 haplotype in about 10% of patients with CD [23, 24, 25]. However, the disease expression, besides

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genetic predisposition and exposure to gluten, also requires the influence of other external factors [1, 23, 26]. Gliadin peptide hydrolysate binds to the HLA class II glycoproteins on antigen-presenting cells (APC) inducing the activation of intestinal CD4+ T-lymphocytes which, by secreting pro-inflammatory cytokines, lead to inflammation of the small intestinal mucosa [23]. This process is preceded by tissue transglutaminase-mediated deamination of the glutamine residue of gliadin hydrolysate, which increases the affinity of their bonding with HLA DQ2 and DQ8 molecules [23]. Humoral immunity also plays a significant role in the pathogenesis of CD, which is confirmed by the presence of autoantibodies to reticulin, endomysium, tissue transglutaminase, and other body structures [22, 23]. The duodenum and the proximal part of the jejunum are most often affected by changes [23]. According to the modified Marsh criteria, inflammation of the small intestinal mucosa is classified into infiltrative, infiltrative-hyperplastic, and destructive [27]. Destructive enteropathy is additionally classified into partial, subtotal, and total.

The symptomatic form of the disease has two modes of clinical presentation (classical and non-classical) and is less frequent compared to the asymptomatic form [1]. In the classical clinical presentation, chronic diarrhea, malabsorption, and secondary malnutrition are most often observed, while in the non-classical form, extraintestinal manifestations such as isolated hypertransaminasemia, constipation, iron deficiency anemia, chronic fatigue, abdominal pain, aphthous stomatitis, short stature and delayed puberty, infertility, enamel hypoplasia, decreased bone density (osteopenia or osteoporosis), polyneuropathy, alopecia, epilepsy, depression, anxiety, and others are most common [1, 17, 23, 28, 29]. Newborns and young children usually have the classic clinical form of the disease, unlike older children and adults. [23]. In CD diagnosed too late or treated inadequately, very serious complications are possible, such as "cell crisis" in children of the youngest age, i.e., total gastrointestinal insufficiency followed by severe hydro-electrolytic and nutritive disbalance, or T-cell small intestinal lymphoma, intestinal adenocarcinoma, ulcerative jejunoileitis and refractory sprue in adults [23, 30].

The main way to diagnose CD is enterobiopsy with subsequent pathohistological analysis of the small intestinal mucosa [31]. According to the latest recommendations of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) defined in 2010, this procedure is necessary not only in patients with symptoms and/or signs corresponding to CD, but also with present IgA antibodies to tissue transglutaminase (AtTG) above 100 U/ml, positive anti-endomysial antibodies and "celiac HLA" (DQ2 and/or DQ8) [32, 33]. The diagnosis of CD could be verified by the clinical recovery and AtTG disappearance after introducing a gluten-free diet [16]. Such attitude in the CD diagnostics is based not only on high sensitivity and specificity of IgA AtTG as a serological marker of the disease (> 95%) but also on a highly significant correlation of their titer with the degree of small intestinal mucosa damage, as well as on the almost unavoidable (> 98%) presence of HLA DQ2 and/or DQ8 [16]. Serological indicators of the disease, such as autoantibodies to endomysium and tissue transglutaminase, and antibodies to deaminated gliadin peptides, have high sensitivity and specificity, but not an absolute diagnostic validity [16]. Therefore, they are primarily used in the detection of asymptomatic and atypical forms of the disease, as well as in the assessment of the consistency of elimination diet in cases with the already verified disease [32]. The latest ESPGHAN criteria recommend gluten provocation test and subsequentional patohistological analysis for confirmation or exclusion of CD in cases where gluten-free diet was introduced before enterobiopsy, in cases where patohistological findings were not typical, and in cases where samples for patohistological analysis were too small or inadequate for final decision. This procedure should not be conducted before the sixth year of life and during puberty because of the negative influence on permanent teeth and growth [16, 31].

Because CD is a lifelong disorder, the gluten-free diet is the foundation of successful treatment [1, 16, 33]. Some additional treatment such as supplementation of iron and folates as well as other vitamins and microelements could be required especially during the initial phase of treatment. Restriction of lactose intake may also be required in some patients [34]. Semi-elementary and/or additional parenteral nutrition, edema removal, and stabilization of the water–salt balance could be required in patients with severe forms of the disease. Sometimes, short-term glucocorticoid therapy is used [35].

GLUTEN ATAXIA

Gluten ataxia (GA) is one of the most frequent and serious gluten-induced autoimmune neurological diseases with clinical presentation mainly in the middle and late adult age [1, 9, 10]. It occurs as a result of damage to the cerebellum as one, and sometimes the only manifestation of the CD [8, 36]. Gluten-induced ataxia also occurs in the absence of CD [37, 38]. Antibody cross-reactivity may be one of the mechanisms involved in GA pathogenesis because of the similarity between gluten proteins and antigenic epitopes on Purkinje cells [36]. Diagnostic delay leads to an irreversible loss of Purkinje cells, followed by permanent neurological damage [8, 39]. GA is most often manifested with dysarthria, pyramidal dysfunction, gait problems, limb ataxia, pyramidal dysfunction, altered eye motion, progressive loss of stability, and inability to stand straight [8, 9]. Less than 10% of GA patients have gastrointestinal symptoms and about one-half have small intestinal histology compatible with CD [39]. Immunoassays of patients with GA show positive IgA and/or IgG antigliadin antibodies, presence of antibodies to TTG2 (from the gut), and TTG6 (from brain tissue) [8]. In most patients at the time of diagnosis, brain magnetic resonance revealed cerebellar atrophy [8, 9]. GA therapy involves a rigorous gluten-free diet throughout life, which reduces disability and prevents further progression of the disease [8, 9, 39]. When the diet does not give satisfactory results, immunosuppressive drugs can be used [37].

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH) is an autoimmune skin disease that usually occurs within CD and manifests with blistering rash and cutaneous IgA deposits. It may present at any age, but it predominantly presents in middle-aged persons [1, 13, 25]. It was found to be more frequent in men than in women, contrary to other autoimmune diseases, but some recent studies point out that sex imbalance may reduce with incising age, and may not be so profound [40]. Also, an Italian large study revealed interesting findings of the high prevalence of DH within the pediatric population, which is usually underreported [13]. DH is characterized by cutaneous lesions that are polymorphic in nature, relapsing and itching, localized on the face, shoulders, knees, elbows, buttocks, and sacral region. Typical CD HLA haplotypes (DQ2 and DQ8) are usual for patients with DH. Although the gastrointestinal symptoms in DH are rare and mild, a higher number of intraepithelial lymphocytes and celiac-type intestinal atrophy are present in almost 70% of patients with apparently normal biopsy findings. Tissue transglutaminase (TTG2) specific autoantibodies could be found in the small bowel mucosa and serum of patients with DH and CD, but skin biopsy in DH shows typical TTG3-(epidermal transglutaminase) targeted IgA antibodies [13]. Strict and timely introduced lifelong gluten-free diet alleviates cutaneous symptoms, improves enteropathy symptoms, and minimizes the risk for complications, especially small intestinal B-cell lymphoma [17]. For the same patients, Dapson helps ease itching and controls the development of cutaneous lesions [17, 41].

WHEAT ALLERGY

Wheat allergy (WA) is IgE-mediated and/or non-IgE-mediated allergic adverse reaction to wheat proteins. According to clinical manifestation, WA can be divided into (1) classical form of food allergy with the involvement of gastrointestinal tract, skin, and possibly respiratory tract, (2) inhalant allergy (Baker's asthma and rhinitis), (3) wheat-dependent, exercise-induced anaphylaxis (WDEIA), and (4) contact urticaria. In Europe, the reported prevalence of WA is 3.6% for all ages [8].

WA is characterized by the following symptoms: skin rash, wheezing, itching, and swelling in the mouth, nose, eyes, and throat (typical IgE-mediated allergy symptoms), gastrointestinal symptoms like cramps, bloating, diarrhea, but WA can sometimes manifest itself with anaphylactic shock. Allergens that most commonly trigger WDEIA are alfa-amylase inhibitors and a subtype of grain protein, ω-5 gliadin [8, 42].

In establishing WA on wheat proteins can be measured by specific IgE antibodies and skin reactions. An oral provocation test is usually required to confirm the diagnosis since the level of specific IgE antibodies and skin reactions exhibit low specificity and sensitivity. A double-blind placebo-controlled trial is considered a gold standard for the diagnosis of food allergy but, in clinical practice, the reduction in symptoms associated with a wheat-free diet indicates that WA is present. In those who have exhibited wheat-induced anaphylaxis, oral provocation should never be done [8, 14].

Usually, patients with WA are not allergic to other cereal prolamines in rye, barley, and oats, and their diet is less restrictive than that in CD. Elimination of wheat products is the basis of treatment of WA. In children with predominant gastrointestinal manifestations, as with other food allergies, 75% of wheat tolerance develops in adolescence [14, 17].

NON-CELIAC GLUTEN SENSITIVITY

In the past decade, non-celiac gluten sensitivity (NCGS) has received growing attention. Studies report that prevalence ranges 0.63–6% due to the challenging diagnosis [4, 42, 43]. The diagnosis of NCGS is established when CD and WA are excluded, and the same improvement in extraintestinal and gastrointestinal symptoms is observed after the introduction of a gluten-free diet [1]. Also, symptoms display significant overlap with irritable bowel syndrome. Although CD and NSGS may have similar symptoms, a careful retrospective investigation revealed that there are some differences in the clinical presentation between NCGS patients and CD patients. nutrient deficiency, malabsorptive symptoms, and autoimmune diseases are rarer in NCGS patients than in CD patients. Abdominal discomfort, bloating, meteorism, diarrhea, 'foggy mind,' fatigue, headache, and joint pain are most commonly reported as symptoms in patients with NCGS [4]. The pathogenesis of the disease is not clear, but some explanations include the activation of the innate immune response and mediation of the immunological system [44]. Regarding genetic susceptibility, HLA-DQ2 and HLA-DQ8 haplotypes could be found in half of the patients with NCGS, which is lower than that in CD patients, but not as low as in the general population [45]. NCGS frequently occurs in parents, siblings, and children of patients with CD, predominantly in females [46]. Serological tests show that more than half of the patients with NCGS have anti-gliadin antibodies (AGA) IgG antibodies in circulation, which disappear after gluten withdrawal. In clinical practice, physicians have to be aware that AGA IgG is not a reliable serologic marker for NSGS because it can be detected in various autoimmune diseases, and among healthy people as well [47]. Although gluten and other protein components of grain cereals (α-amylase trypsin inhibitor) can be responsible, they are not the only ones that could cause symptoms. Some grains and cereals are rich in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), which can cause gastrointestinal symptoms as well. Intake of food with low levels of FODMAPs can lead to a significant reduction in symptoms even if gluten has not been eliminated from the diet. Although groceries without gluten often have low levels of FODMAPs, patients recognized as NCGS suffer from irritable bowel syndrome with symptoms resulting from consuming FODMAPs rather than gluten [17].

For now, the diagnosis is still based only on the exclusion of CD and WA in addition to the double-blind placebo-controlled study, which is ideal but not always possible in clinical practice [17]. Starting a gluten-free diet establishes improvement in most patients, but the diet does not need to be strict, because inadvertently introduced traces of gluten usually do not cause symptoms [4, 8]. It is still unknown whether NCGS is a permanent condition in all patients [48, 49, 50].

CONCLUSION

GRDs make a heterogeneous group of clinical entities caused by genetically determined intolerance to wheat, rye, and barley flour components. After an adult form of lactose intolerance, GRDs are the most common food-related disorder. The pathogenesis of CD, GA, and DH is based on the gluten-activated autoimmune process, of WA on IgE- and/or non-IgE-mediated reaction to gluten and other proteins of said cereals, while NCGS is the result of stimulation of the innate immunity and some non-immunological mechanisms. The basis of treatment of GRDs is gluten-free diet. The condition is lifelong for the autoimmune forms of the disorders; WA, especially if it occurs in the youngest age, is mostly transitory. For now, it is not clear whether all patients with NCGS must be on lifelong gluten-free diet.

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Поремећаји везани за глутен

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САЖЕТАК

Поремећаји везани за глутен су хетерогена група клинички ентитета који настају услед неподношења компонената пшеничног, јечменог и раженог брашна и испољавају се обично код генетски предиспонираних особа. На основу патогенетских и клиничких карактеристика класификују се на целијачну болест, алергију на пшенично брашно и нецелијачну осетљивост на глутен. Као специфични ентитети, присутни у оквиру целијачне болести или без ње, издвајају се глутенска атаксија и херпетиформни дерматитис. У овом чланку, базираном на савременим сазнањима, приказани су основни детаљи везани за патогенезу, клиничку експресију, дијагностику и терапију ових поремећаја.

Кључне речи: целијачна болест; глутенска атаксија; херпетиформни дерматитис; алергија на пшенично брашно; нецелијачна глутенска сензитивност