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Spectrum of gluten-related disorders: celiac disease, wheat allergy, baker's asthma and non-celiac gluten sensitivity

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ABSTRACT

Gluten, which is a protein found in wheat, can trigger some gastrointestinal diseases in people with genetic predisposition. Gluten related disorders include celiac disease (CD), wheat allergy, baker's asthma and non-celiac gluten sensitivity (NCGS). Approximately 1% of population suffers from celiac disease. It is believed, that the occurrence of the disease is determined by the interaction of genetic, immunological and environmental factors. The consequence of the inflammatory process is the atrophy of the intestinal villi. That results in impaired bowel motility, improper digestion and impaired absorption of substances contained in the diet. Wheat allergy occurs among people with a genetic predisposition to allergies. People with this disorder are sensitized to products containing gluten and every contact with this antigen leads to mast cell activation and the release of mediators of the allergic reaction - mainly histamine. They mainly affect the skin (urticaria, atopic eczema, angioedema), digestive system (nausea, vomiting, spasmic abdominal pain) and respiratory tract (asthma, allergic rhinitis). Baker's asthma is an interesting and common allergic, occupational disorder related to inhalation of flour containing gluten. The main symptoms include: conjunctivitis, rhinitis, dermatitis, as well as work-related cough and dyspnea. First reports on non-celiac gluten sensitivity (NCGS) appeared in 1980. The diagnosis of non-celiac gluten sensitivity is based on the exclusion of celiac disease and food allergy in a patient who has symptoms induced by ingestion of gluten. The exact pathomechanism of this disease is still unknown. Interestingly, some researches doubt that this

disorder is caused by gluten intake. All of the above-mentioned diseases have a similar spectrum of clinical symptoms, and as part of the treatment require an elimination diet with the exclusion of gluten. The aim of this study is to provide information on gluten-related diseases, taking into account their pathomechanism and clinical picture.

Keywords: gluten, celiac disease, wheat allergy, non-celiac gluten sensitivity

1. INTRODUCTION

In recent years the popularity of a gluten-free diet has increased significantly. Studies show that gluten is avoided more often than the real occurrence of a medically confirmed diseases associated with its consumption [1-3]. The growth in interest and an increasing desire of gluten-free diet is undoubtedly caused by a certain fashion and widespread advertising of gluten-free products. It also correlates with the increase in the number of people affected by gluten-dependent diseases, mainly: celiac disease, wheat allergy and non-celiac gluten hypersensitivity [4]. It is worth noting that, despite the common etiological factor, these diseases differ significantly.

The purpose of the following work is to summarize the information available in the medical literature about the aforementioned diseases.

2. GLUTEN

Gluten is a conventional name for a protein complex that is formed from the combination of plant proteins: prolamins and glutelins. These molecules are contained in cereals and combine with each other while kneading the dough with flour and water. Prolamines are a large and heterogeneous group, including gliadin (present in wheat), secalin (present in rye), hordein (in barley) and avenin (in oats) [5].

Gluten plays an important role in technological processes related to baking bread. During kneading, as a result of cross-linking, it creates a spatial structure that gives the knead a flexibility. What is more, because of gluten, the bread grows better, takes on a porous, elastic structure and becomes stale later than gluten-free bread [6].

3. GLUTEN-RELATED DISORDERS

3. 1. Celiac disease

Celiac disease (also known as “*coeliac disease*” or “*celiac sprue*”) is a chronic, autoimmune disease of the small intestine. The consumption of gluten in genetically predisposed individuals leads to the damage of the small intestine mucous membrane and, as a result, to the occurrence of disturbances in the absorption of nutrients. Symptoms can manifest at any age, both in children and in the adults [7]. Currently, celiac disease is mostly detected in people in the age of between 30 and 50 years. According to statistics, this disease affects 1% of the population, with women suffering twice as much as men [8].

The pathogenesis of celiac disease is multifactorial. It is believed, that the occurrence of the disease is determined by the interaction of genetic, immunological and environmental factors. Genetic predisposition is associated with the occurrence of the HLA-DQ2 or HLA-DQ8 genotype [9]. HLA are human molecules of the main complex of human leukocyte antigens, which are involved in the modulation of the body's immune response. Each person has their own genetically conditioned and very diverse set of HLA molecules. In the correct conditions, proteins that are foreign to the body, i.e. antigens (e.g. bacterial fragments), are attached to HLA and are then presented to T lymphocytes. In this way, the immune system is activated and destruction of what led to the start of the reaction [10]. Differences between HLA molecules are mainly expressed in changes in the antigen-binding site. The greater the diversity, the greater the potential for binding and presentation of antigens and hence - better immunity. In the case of celiac disease, the protein presented by HLA-DQ2 / HLA-DQ8 is gluten or peptides uprised from its digestion [11]. The immune system recognizes them as foreign and thereby activates the immune cascade to produce proinflammatory cytokines and specific antibodies against: epithelial membrane antigen (EmA), tissue transglutaminase (tTG) and deaminated gliadin peptides (DGP) [12,13]. Increased inflammation causes damage and death of intestinal epithelial cells. The consequence of this process is the atrophy of the intestinal villi, which results in impaired bowel motility, improper digestion and impaired absorption of substances contained in the diet (Figure 1).

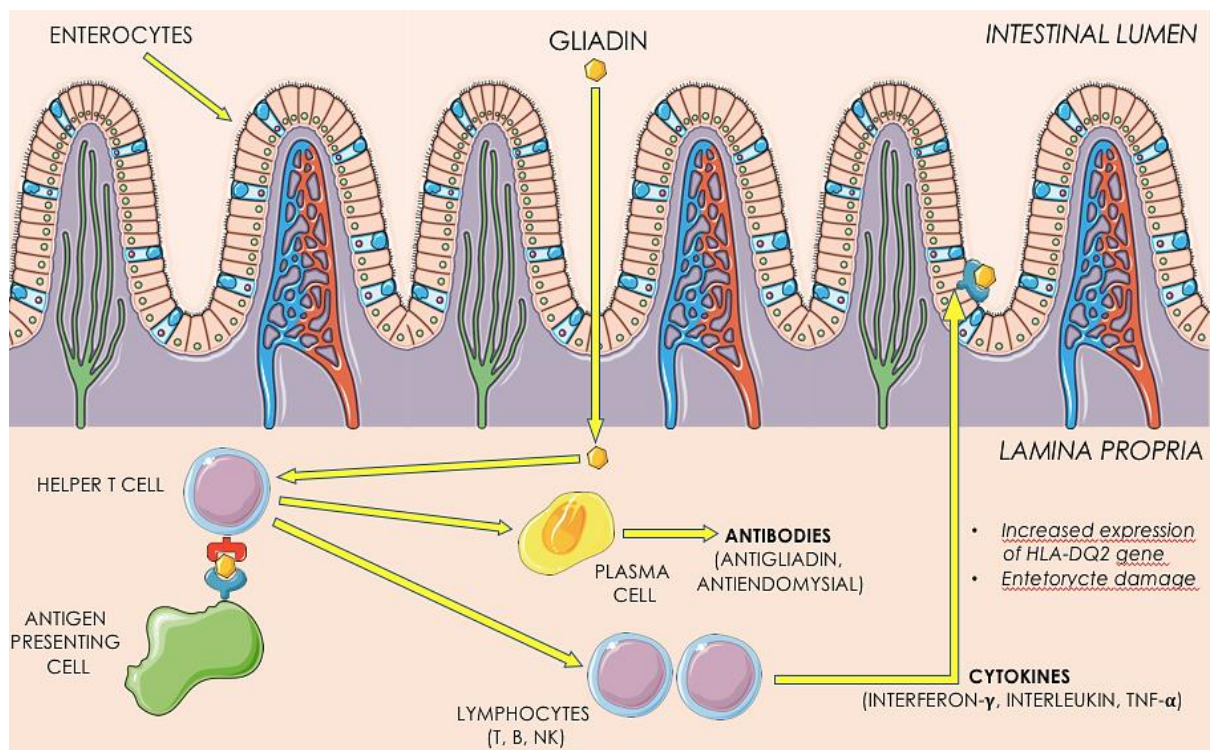


Figure 1. Schematic illustration of celiac disease pathomechanism

Genetic load is an important predictor of celiac disease development, but its determination is not synonymous with the diagnosis of the disease [14,15]. HLA-DQ2

haplotype is expressed in about 90-95% of patients with celiac disease, but is also present in 20-30% of the healthy European population [16]. This fact indicates the coexistence of other, previously unknown, genetic factors that are necessary for the development of the disease.

The main environmental factor conditioning the development of celiac disease is exposure to gluten. For predisposing individuals, the prolamines contained in wheat (gliadin), rye (secalin) and barley (hordein) are particularly toxic [17]. Avenin contained in oats does not induce such an intensified inflammatory reaction as the above-mentioned prolamins, however obtaining pure oat products that do not contain admixtures of other cereals is very difficult. Therefore, their consumption is also contraindicated. The exception is products containing certified gluten-free oats from pure crops [18].

In the medical literature, much attention is paid to the discussion on the time of gluten introduction into the infant's diet in the context of the risk of developing celiac disease. It is now believed that gluten should be introduced in a small, gradually increasing dose, between 4 and 7 months of age [19]. Previous research suggests that the early introduction of gluten into the child's diet does not increase the risk of celiac disease, although the late introduction of gluten-containing products may pose such a risk [20]. Gluten can be introduced into the diet of infants from the age of 4 months (or 17 weeks) until the age of 12 months. It seems that the introduction of gluten in this age range does not affect the absolute risk of developing celiac disease or celiac autoimmunization [21].

The list of clinical symptoms that may occur in celiac disease is very long. Often the symptoms are uncharacteristic and therefore cause difficulties in making the right diagnosis. It is particularly difficult to diagnose celiac disease in adults who may be dominated by non-intestinal symptoms. According to data collected by the University of Oxford, the waiting time for making a diagnosis of celiac disease in the UK is on average 13 years [22]. In other countries, early diagnosis of celiac disease also causes many difficulties for doctors.

According to current medical knowledge, there are four clinical forms of celiac disease:

- 1) The classic form - in which gastrointestinal symptoms predominate, most often chronic fat or watery diarrhea, abdominal pain, bloating, vomiting and weight loss or malnutrition.
- 2) Atypical form - in which extraintestinal symptoms predominate, patients may experience constant fatigue, change of temperament (hyperactivity or fatigability and apathy), depressive states and delay in sexual maturation in children.
- 3) Silent form - which is asymptomatic, but leads to damage to the mucous membrane of the small intestine and villus atrophy, which can be stated during duodenal biopsy.
- 4) Latent form - also asymptomatic, but without damage to the intestinal mucosa. Patients do not show any clinical symptoms or changes in the gut, but there are antibodies in the blood that are characteristic for celiac disease and can develop with venous damage at any time.

All the above-mentioned symptoms are uncharacteristic and difficult to connect with celiac disease. Often the disease develops secretly and for many years remains undiagnosed. The division into clinical forms is made on the basis of the prevailing symptoms. Each patient may have different combinations of both intestinal and extraintestinal symptoms [23].

Celiac disease diagnostics is based on serological tests and small intestinal biopsies [24]. Since maintaining a gluten-free diet results in the remission of symptoms and a reduction in the antibodies level in the blood, patients should consume at least one gluten-containing meal every day for 6 weeks before performing the tests [25]. Currently, studies are carried out to detect a diagnostic method that will enable the diagnosis of celiac disease without the need to intestinal biopsy [26]. One of the methods proposed is the detection of activated (by HLA molecules that present gluten fragments) of serum T lymphocytes, but this method still requires many additional tests [27]. When initiating diagnostics, blood serum should be evaluated for the presence of specific IgA antibodies against smooth muscle endomysium (EmA) and tissue transglutaminase (tTG).

It is also necessary to determine the total level of IgA antibodies in the serum to determine if their level is normal. A deficiency of IgA antibodies may lead to false negative results. In people with IgA deficiency, IgG antibodies are recommended [28-30]. Importantly, negative serological results do not exclude celiac disease. Among the adult population to make a diagnosis it is necessary to perform a small intestinal biopsy and to find characteristic inflammatory changes in the intestinal mucosa along with the disappearance of the villi. The changes introduced by the European Society of Gastroenterology, Hepatology and Child Nutrition (ESPGHAN) from 2012, introduced the possibility to refrain from carrying out an intestinal biopsy in children, provided by: confirmed, clinical symptoms of the disease, at least a ten-fold increase in serum tTG antibodies and EMA antibodies in a separate blood sample, as well as the presence of the HLA-DQ2 / HLA-DQ8 isoform in the genetic analysis [31].

The basic method of celiac disease treatment is to completely exclude gluten from the diet. Failure to comply with dietary recommendations or late diagnosis of celiac disease may result in serious complications. Complications associated with malabsorption may occur, such as deficiency diseases such as osteoporosis, anemia due to iron / B12 deficiency or short stature. Patients may also have mental and neurological disorders [32]. It also increases the risk of developing autoimmune and cancer diseases - throat, esophageal, small intestine and intestinal lymphoma. Celiac disease is a lifelong disease, therefore it requires strict adherence to medical recommendations to eliminate clinical symptoms and to avoid serious consequences [33].

3. 2. Wheat allergy

Wheat allergy is a disease, which belongs to the group of food allergies. Therefore, its pathomechanism is completely different than celiac disease and is based on an allergic reaction and not an autoimmune reaction [34]. Products that most often cause food allergies are: cow's milk, eggs, cereals (mainly wheat), soy, fish, crustaceans, nuts and peanuts [35]. The development of the allergic process is complex and occurs in people with a genetic predisposition to allergies. It is worth noting that the food we eat is a foreign substance to the body and naturally stimulates the cells of the immune system. However, in normal conditions, thanks to the mechanisms referred to as "food tolerance", the immune response suppresses. In people who develop food allergy this mechanism does not work properly and sensitize to a given food allergen. Sensitization consists in the production of specific IgE antibodies, which upon re-contact with a given antigen can lead to mast cell activation and the release of mediators of the allergic reaction - mainly histamine. Symptoms of food allergy appear within a few minutes or a few hours after consumption of the product and mainly affect the skin

(urticaria, atopic eczema, angioedema), digestive system (nausea, vomiting, spasmic abdominal pain) and respiratory system (asthma, allergic rhinitis) [36]. A fatal consequence of food allergy may be the occurrence of life-threatening anaphylactic reaction. In the case of allergy to wheat, the main allergens include α -amylase / trypsin inhibitors and ω -5 gliadin, which is an element of gluten [37].

According to the recommendations of the European Society of Gastroenterology, Hepatology and Children's Nutrition (ESPGHAN), the diagnosis of food allergy is based on the accurate collection of clinical history, determining what food and in what dose causes an allergic reaction and on a thorough physical examination [38]. It is also recommended to perform a provocative test, subject to the decision on its implementation belongs to the doctor and is strictly dependent on the patient's state of health and age [39]. The diagnosis also includes the determination of the amount of specific IgE in the blood serum and skin prick tests. Treatment of food allergy, like in celiac disease, is based on the use of an elimination diet. After diagnosing allergy to wheat, all products containing it must be excluded from the diet. However, due to the fact that the food allergy may be transient, especially in the first years of life, it is recommended to repeat the provocative test at appropriate intervals. In the case of severe anaphylaxis, the treatment is based on the use of adrenaline and advanced medical procedures that maintain the efficiency of the respiratory and cardiovascular systems [40].

3. 3. Baker's asthma

Occupational exposure to flour dust concerns employees of the food industry and food production. It promotes the development of various clinical conditions - from conjunctivitis to so-called bakers' asthma (baker's allergy) [41].

Well-known since the Roman Empire times, baker's asthma is an allergic reaction caused by the inhalation of wheat flour. Symptoms of the disease are found in 10-15% of bakers [42]. An exposure to flour dust occurs also in pasta factories, pizza bakeries, confectionery, restaurants, malt factories and animal feed plants. The disorder may also develop in patients who consume contaminated or unprocessed wheat flour products [43].

Flour dust usually contains various components which act an important role in dough improvement, for example: variety of enzymes (α -amylase, cellulase, hemicellulase, malt enzymes, xylanase, protease, lipase, glucoamylase, glucose oxidase, lipoxxygenase), additives (baker's yeasts, egg powder, milk powder, sugar), flavorings, spices and chemical ingredients. It may also comprise of storage-related contaminants, such as microbes or mites. The main cereal used in the bakery industry is wheat. Wheat flour contains four groups of proteins: glutelins (glutenins), water-soluble albumins, prolamins (gliadins) and globulins. Glutenins and gliadins are molecules which form gluten [44].

In addition, a gluten-extrinsic allergen has been identified as aspergillus amylase, added to flour to increase its baking characteristics [45]. Sander et al. indicates that wheat flour is comprised of 40 allergens at least, which can cause adverse health effects in exposed workers [46]. The fungal α -amylase (in wheat or derived from *Aspergillus oryzae* or *Aspergillus niger*, added to improve baking characteristics), thioredoxin, serine proteinase inhibitor, thaumatin-like protein, fructose-bisphosphate aldolase, glycoprotein with peroxidase activity, triose-phosphate isomerase and prolamins are the main factors associated with asthma among workers exposed to baking flour [47].

A symptomatic sensitization to flour and other bakery ingredients arise relatively quick – usually within the first year of exposure. One of the primary mechanisms is immunoglobulin E (IgE) immediate hypersensitivity reaction. It develops shortly after exposure to the antigen, which can be evidenced by tests (positive skin tests or serum radioimmunoassay tests) [48]. The main symptoms occurring in baker's asthma are: conjunctivitis (red eye, swelling of the conjunctiva, itching and watering of the eyes), rhinitis (sneezing, nasal itching, coughing, headache) and different types of contact dermatitis (allergic, irritant) [49,50]. Chronic exposure to flour dust may also lead to pathological abrasion of hard teeth tissues. The dust adhering to the teeth surface and gum edge creates a specific coating, which causes hard tooth tissue earlier abrasion [51].

Due to the multitude of factors involved in the pathogenesis of baker's asthma, the disease still requires careful research.

3. 4. Non-celiac gluten sensitivity

The first references on non-celiac gluten sensitivity (NCGS) appeared many years ago. In 1980, British physicians Cooper et al. Described the cases of 8 women aged 24-47 with clinical symptoms of celiac disease, but without changes in the structure of the small intestinal mucosa characteristic for it [52]. The published work, together with an attempt to introduce a new disease, did not find support among the medical community and were widely criticized. Therefore, the topic of non-celiac gluten sensitivity disappeared from scientific publications for many subsequent years. However, every year, the increasing number of patients was noticed, in whom celiac disease and wheat allergy were excluded, and symptoms of the diseases mentioned above were found. What is more, the introduction of a gluten-free diet resulted in the improvement of patients clinical condition. Due to the increase in social interest in this topic, NCGS returned to the medical literature. There are still many studies that aim to determine the exact etiology and pathomechanism of this disease.

The diagnosis of non-celiac gluten sensitivity is based on the exclusion of celiac disease and food allergy in a patient who has symptoms induced by ingestion of gluten [53]. The frequency of this disease is unknown. Depending on the source, it is assumed to affect 0.5-6% of the population. It can occur at any age [54]. The most frequently described symptoms are: abdominal pain and flatulence, unjustified anxiety and sleep disturbances, headache, fatigue, diarrhea, skin changes [55]. It is impossible to distinguish NCGS from celiac disease on the basis of clinical symptoms [56]. Currently, there are no immunological or clinical tests to diagnose the disease. Diagnosis is based on the exclusion of other forms of gluten intolerance [57]. Etiology and pathomechanism are not sufficiently known. Interestingly, in the scientific literature there are more and more reports suggesting that it is not gluten but other substances contained in food that can cause symptoms of the disease. As the etiological agents are often mentioned fermented oligo-, di- and monosaccharides and polyols – the so called FODMAPs [58,59]. According to scientists, due to the easy fermentation of polyols and their osmotic effects in the intestines, predisposed persons may experience increased gas production and flatulence [60].

Due to the large amount of vaguenesses, non-celiac gluten sensitivity still requires many additional studies and long-term observations to determine the causes of its occurrence and introduce simple diagnostic tests.

4. CONCLUSIONS

The four main disorders associated with gluten intolerance are: celiac disease, wheat allergy, baker's asthma and non-celiac gluten sensitivity. Despite the common triggering factor, these diseases are characterized by a completely different pathomechanism. Celiac disease belongs to autoimmune diseases, wheat allergy and baker's asthma are an allergic disorders, and non-celiac gluten sensitivity does not represent neither autoimmunological nor allergic diseases.

All of the above-mentioned diseases have a similar spectrum of clinical symptoms, and as part of the treatment require an elimination diet with the exclusion of gluten.

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