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Целиакия, аллергия к пшенице, нецелиакийная чувствительность к глютену: актуальные вопросы патогенеза и диагностики глютенассоциированных заболеваний

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АННОТАЦИЯ

Традиционно потребление пшеницы и других глютенсодержащих круп является важной частью диеты большинства людей во всём мире. Однако широкое распространение глютенсодержащих продуктов привело к увеличению случаев побочных реакций, связанных с их потреблением, — целиакии, аллергии на пшеницу, а также распространённой в последние годы нецелиакийной чувствительности к глютену.

Глютенассоциированные заболевания обладают во многом схожими клиническими проявлениями (боль в животе, вздутие, диарея, тошнота, рвота), при этом патогенетические механизмы, лежащие в основе целиакии и аллергии на пшеницу, достаточно хорошо изучены (в обоих случаях возникает иммунный ответ при употреблении белков пшеницы), и разработаны эффективные методы их лечения. В то же время нецелиакийная чувствительность к глютену является предметом дискуссий, нет полного понимания процессов, лежащих в основе этого заболевания, и, соответственно, единого подхода к диагностике и лечению. На сегодняшний день нецелиакийная чувствительность к глютену является диагнозом исключения, который устанавливается при отсутствии маркеров целиакии или аллергии на пшеницу и улучшении самочувствия на фоне безглютеновой диеты.

Безглютеновая диета является наиболее эффективным методом лечения глютенассоциированных заболеваний, но, как и любые строгие ограничения в питании, полный отказ от потребления глютена может приводить к снижению поступления таких важных питательных веществ, как пищевые волокна, белок, микронутриенты. В последние годы многие люди, не консультируясь с врачом, сами устанавливают себе диагноз нецелиакийной чувствительности к глютену и отказываются от его потребления по собственному желанию, что связано с распространённым, но не обоснованным научно предположением о токсичности глютена для человека.

Согласно существующим рекомендациям, только подтверждённый диагноз целиакии и аллергии на пшеницу является основанием для соблюдения строгой безглютеновой диеты.

Обзор посвящён современной концепции иммунологических реакций, лежащих в основе глютенассоциированных заболеваний, и предполагаемых перспектив в развитии методов лечения.

Ключевые слова: аллергия; целиакия; глютен; глютеновая чувствительность; пшеница.

Как цитировать

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Celiac disease, wheat allergy, and nonceliac sensitivity to gluten: topical issues of the pathogenesis and diagnosis of gluten-associated diseases

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ABSTRACT

Historically, wheat and other gluten-containing grains have been an essential part of the diet of many people worldwide. However, the widespread use of gluten-containing products has led to an increased incidence of adverse reactions associated with their consumption, such as celiac disease and wheat allergy, as well as nonceliac gluten sensitivity, which has become common in recent years.

Gluten-associated diseases have similar clinical manifestations (abdominal pain, bloating, diarrhea, nausea, and vomiting). The pathogenetic mechanisms underlying celiac disease and wheat allergy are quite well understood; in both cases, an immune response occurs when wheat proteins are consumed, both with effective treatment. Nonceliac gluten sensitivity is the subject of discussion; however, the processes underlying this disease are not fully understood; thus, its diagnosis and treatment have no unified approach. To date, nonceliac gluten sensitivity is a diagnosis of exclusion, which is established in the absence of markers of celiac disease or wheat allergy and improved following a gluten-free diet.

A gluten-free diet is the most effective treatment for gluten-related diseases. However, like any other strict dietary restriction, gluten avoidance can result in reduced intakes of important nutrients, such as dietary fiber, protein, and micronutrients. In recent years, an increasing trend is found in the general population without confirmed gluten-related disorders that gluten-free product consumption or gluten-free diet adherence since gluten avoidance can improve well-being or gluten can be toxic for all human beings

According to current guidelines, only patients diagnosed with celiac disease or wheat allergy are advised to follow a strict gluten-free diet.

Herein, the modern conception of the immunopathology of gluten-related diseases and an overview of new potential therapies are presented.

Keywords: allergy; celiac disease; gluten; gluten-free; gluten sensitivity; wheat.

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ECO•VECTOR

BACKGROUND

Over the past 10,000 years, gluten-containing grains have become an essential part of most people's diets globally. Gluten and gluten-like peptides are the main storage proteins of wheat, including cereals, such as rye and barley, in malt, triticale, and Oriental wheat. Additionally, the high consumption of gluten-containing cereals is associated with the grain's adsorption capacity by providing a stable elastic structure during the preparation of various products, combined with the exceptional organoleptic properties.

However, recently, the widespread use of gluten-containing products has increased the adverse reactions associated with their consumption, such as celiac disease, wheat allergy, and non-celiac gluten sensitivity [1]. These are generally referred to as gluten-associated diseases.

The most effective treatment for gluten-associated diseases is a gluten-free diet. Like other severe dietary restrictions, total abstinence of gluten results in a reduced intake of essential nutrients such as dietary fiber, protein, and micronutrients [2]. However, a gluten-free diet is becoming more common in the general population since this type of nutrition is a healthy choice that enhances weight loss [3]. Many people do not consume gluten and, without consulting a doctor, self-diagnose non-celiac gluten sensitivity since not all doctors recognize the disease's existence with no knowledge of what can be offered to patients [4, 5]. Although there is a clear understanding of the pathogenesis of diseases, such as celiac disease and wheat allergy, the research on non-celiac gluten sensitivity has only just begun.

Therefore, identifying the mechanisms of gluten-associated disease development will provide a fundamental understanding of the adverse reactions of gluten in different groups of patients and allow the development of more precise recommendations for treatment selection and new drug development.

CELIAC DISEASE

Celiac disease is an autoimmune disease characterized by the development of atrophy of the small intestinal mucosa when patients with a genetic predisposition consume gluten. The disease prevalence is approximately 0.5%–1% in the general population [4, 6].

RISK FACTORS

The disease's most studied genetic risk factor is the expression of major histocompatibility complex (MHC) class II proteins, HLA-DQ2 and HLA-DQ8. The HLA-DQ2 haplotype is detected in most patients with celiac disease, whereas DR-4-DQ8 is detected in other cases [7]. These specific changes in MHC proteins are the most critical risk factors and are significant in developing the autoimmune process in celiac disease. Additionally, polymorphisms of the IL-2 and IL-21 genes, namely, cytokines, have been identified to contribute to the inflammatory process in celiac disease, including the disease predisposition [8]. Additional risk factors are low microbiota diversity and viral infections [9, 10]. Research suggests that viruses that cause intestinal infections, such as reoviruses and other species, disrupt the intestine's immune homeostasis and provoke autoimmune reactions [10].

Furthermore, the consumption of gluten and gluten-like proteins is the main environmental factor influencing the development of celiac disease [7]. Gluten is partially hydrolyzed in the digestive system after consumption, forming native peptides, which do not undergo further proteolysis, consequently penetrating the small intestine submucosa. These peptides include α-, ω-, γ-gliadins, gluten derivatives from various wheat cultivars, and gluteins from other cereals, such as hordein found in barley and secaline from rye that both undergo deamination by transglutaminase 2 (also called tissue transglutaminase, TG2) [11, 12]. Notably, deaminated peptides have a high affinity for the DQ2 and DQ8 molecules of the antigen-presenting cells [13]. According to research results, the severity of this process is higher for modern wheat varieties than for those previously used [14].

IMMUNOLOGICAL REACTIONS BASED ON CELIAC DISEASE

The interaction of deaminated peptides with HLA DQ2 and DQ8 receptors of antigen-presenting cells activates the T-lymphocytes. The process releases pro-inflammatory factors such as interferon-gamma, tumor necrosis factor (TNF-α), and interleukin-2 (IL-2). Also, this inflammatory process occurs in the intestine, causing atrophy of the small intestine villi and deep tissue damage [15]. The intestinal intraepithelial lymphocytes also contribute to the development of this condition. The emergence of the gluten-specific generation of CD4+ T-lymphocytes forms a stable local immune response. The CD4+ T-lymphocytes produce a large amount of TNF-γ, IL-2, and IL-21 upon contact with gluten, contributing to the inflammatory process [16]. Furthermore, a critical link in the celiac disease pathogenesis is also an impairment of the limitation of inflammation. Although the count of regulatory T cells does not change in celiac disease, *in vitro* studies showed reduced functional activity [17]. Figure 1 illustrates celiac disease pathogenesis.

The contribution of TG2 (transglutaminase-2) in celiac disease development is not limited to the deamination of gluten-like peptides but to the role of the enzyme as a target for antibody production [18]. Typically, antibodies against TG2 are not produced; however, there are specific B-lymphocytes against TG2. The production of antibodies is encouraged by the gliadin-specific CD4+ T-lymphocytes, especially when the gliadin and TG2 are bound to the small intestinal mucosa [19]. IgA and, to a lesser extent, IgM and IgG mainly represent antibodies against TG2. The level of antibodies does not reduce the enzyme activity despite their high affinity to TG2 [20]. Additionally, there is evidence that

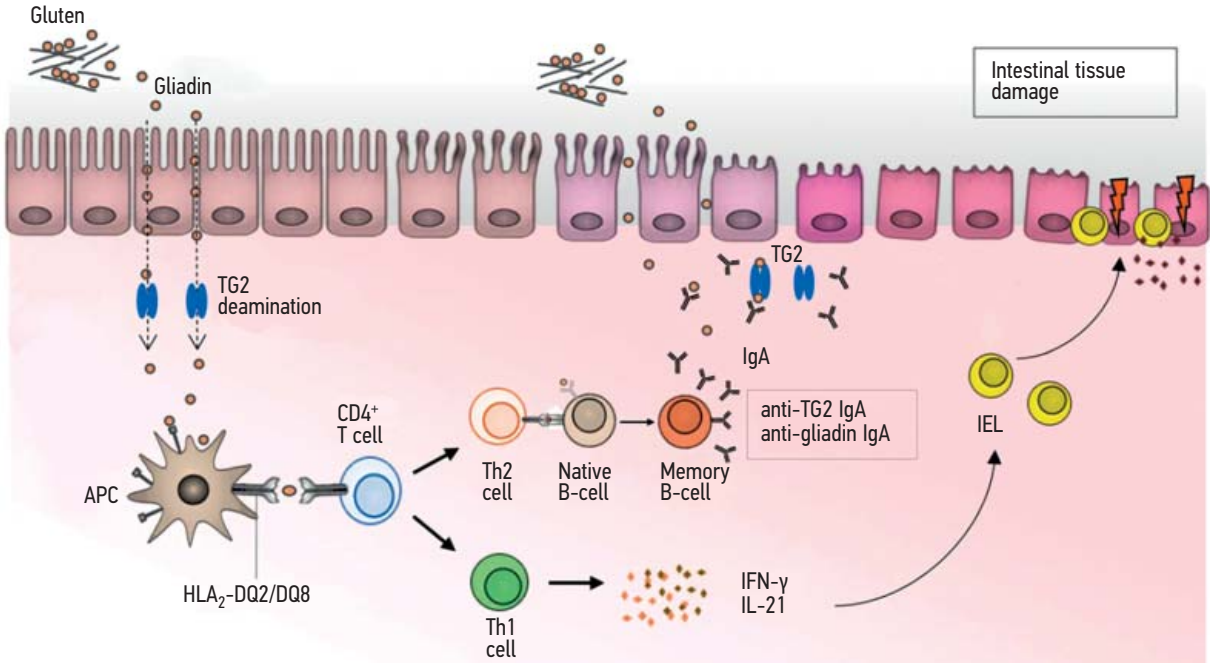

Fig. 1. Pathogenesis of celiac disease. After deamination of gluten peptides process of antigen-presentatiom begins. HLA_2-DQ2/DQ8 in antigen presenting cells (APC) present this peptides to $CD4^+$ T-cells which are key in the initiation of the inflammatory response. On one hand, they promote a Th1 response in which large amounts of IFN-γ and IL-21 are produced contributing to the activation of Intestinal intraepithelial lymphocytes (IELS). $CD4^+$ T-cells also induce a Th2 response and promote the clonal expansion of B-cells and production of IgA antibodies against TG2 and gliadin.

antibodies encourage the mobilization of Ca2+, which induces intracellular activation of TG2 [21]. Although the final role of antibodies to TG2 in celiac disease development is unclear, a direct relationship has been established between the level of autoantibodies and the severity of the inflammatory process in the intestine [22]. Moreover, anti-TG2 IgA represents a specific and sensitive marker of celiac disease usually detected in almost all patients [23].

CLINICAL PRESENTATION, DIAGNOSTICS, AND TREATMENT OF CELIAC DISEASE

Celiac disease occurs in people of any age, with the most common symptoms of either transient or permanent abdominal pain and diarrhea. Also, nausea, bloating, and weight loss are recorded [7, 24]. Common extraintestinal manifestations include fatigue, iron deficiency, and dermatitis herpetiformis [24–26]. Furthermore, low bone mineral density due to malabsorption syndrome is detected in children during celiac disease diagnosis and, in severe cases, causes fractures and osteoporosis in adults [27]. The frequent characteristic neurological complications of celiac disease are interconnected with the level of autoantibodies against TG2 [28, 29]. Additionally, more frequent development of other autoimmune diseases (Type 1 diabetes mellitus, Addison's disease, etc.) characterize patients with celiac disease [30, 31].

Serological tests and biopsy of the duodenum's post-bulbar region diagnose celiac disease. Blood screening for IgA to TG2, which is considered the high specificity and sensitivity of the analysis, is recognized as the method of choice [24, 31]. However, in IgA-deficient patients, such an analysis is uninformative; therefore, it requires alternative options such as the determination of IgG to TG2, IgG to EMA, and IgG to deamidated gliadin peptides. It is recommended to confirm the diagnosis with biopsy when a positive serological test result is obtained in adults. Conversely, determining the HLA genotype is not required when detailed histological results are obtained. Additionally, a duodenal biopsy is not mandatory in pediatric patients with a typical clinical presentation of the disease with a high titer of IgA to TG2 (above 10 times higher than normal), the presence of antibodies against the endomysium and the HLA genotype predisposing patients to the development of celiac disease [31].

The general treatment for celiac disease is a strict gluten-free diet over a lifetime. However, alternative therapies are being developed, given the new data on the pathogenetic mechanisms of celiac disease. For example, during a phase III study, the drug larazotide acetate, which prevents the translocation of gluten through the mucosal barrier, was efficient in decreasing the severity of gastrointestinal symptoms in celiac disease compared with placebo [32]. A new drug, latiglutenase, a non-immunogenic protease that breaks down gluten into small peptides, is also being studied [33]. Additionally, creating vaccines that will allow modeling the work of gluten-specific T-lymphocytes [34] and monoclonal antibodies to block pro-inflammatory cytokines involved in intestinal damage in celiac disease is being considered [35].

WHEAT ALLERGY

IMMUNOLOGICAL REACTIONS BASED ON ALLERGIC REACTIONS TO WHEAT

Celiac disease and wheat allergy (WA) similarly involve an immune response after consuming wheat proteins. However, WA is based on an IgE-mediated reaction, which does not occur in similar proteins of cereals like barley or rye [36]. The initial stage of WA formation is the interaction of wheat proteins as an antigen with antigen-presenting cells. After that, the Th2 cells are formed, releasing pro-inflammatory factors IL-3 and IL-13, consequently activating the proliferation and differentiation of B-lymphocytes and stimulating IgE production. During the repeated interaction with the allergen, the IgE binds to its FceRI receptor located on basophils and plasma cells, followed by the activation of the inflammatory and vasoactive mediators and the development of inflammation, whose generalization is limited both by a local reaction, leading to a severe systemic response. Figure 2 illustrates the mechanism of WA development.

CLINICAL PRESENTATION, DIAGNOSTICS, AND TREATMENT OF ALLERGIC REACTION TO WHEAT

In most patients, WA is most often diagnosed in children since its allergic reaction resolves at school age [37, 38]. According to different authors, the prevalence of WA varies from 0.33–1.17% [4, 5]. Also, various clinical presentations dependent on the age group characterize WA. The most common manifestations include vomiting, abdominal pain, urticaria, angioedema, anaphylaxis, skin rashes, and respiratory symptoms (baker's asthma). Despite the low prevalence of WA in adults, the most common anaphylaxis occurs during physical activity (sometimes the intake of aspirin) or after eating wheat (exercise-induced wheat anaphylaxis). The mechanism of wheat anaphylaxis induced by exercise is attributed to the increased permeability and absorption of allergens in the intestine during intense exercise [39].

Furthermore, baker's asthma is a common occupational disease caused by the inhalation of raw wheat flour [40]. This allergy manifests itself as rhinitis, patients who have asthma symptoms, sometimes conjunctivitis, and skin rashes. However, the consumption of cooked food does not cause symptoms [41, 42].

WA diagnostics is based on detailed case history taking, assessment of clinical manifestations, and laboratory confirmation. A blood test for specific IgE to wheat and skin scratch tests are used as an initial examination. In cases of suspected WA associated with wheat consumption, the gold standard for confirming allergy is a double-blind, placebo-controlled oral challenge test. This test is considered safe; however, it is performed with the involvement of medical personnel due to the possibility of anaphylactic reactions [43].

Diagnostics of exercise-induced wheat anaphylaxis are more complex and involve taking a detailed history and testing for wheat IgE and, in some cases, a challenging exercise test after wheat consumption [44, 45]. Simultaneously, the

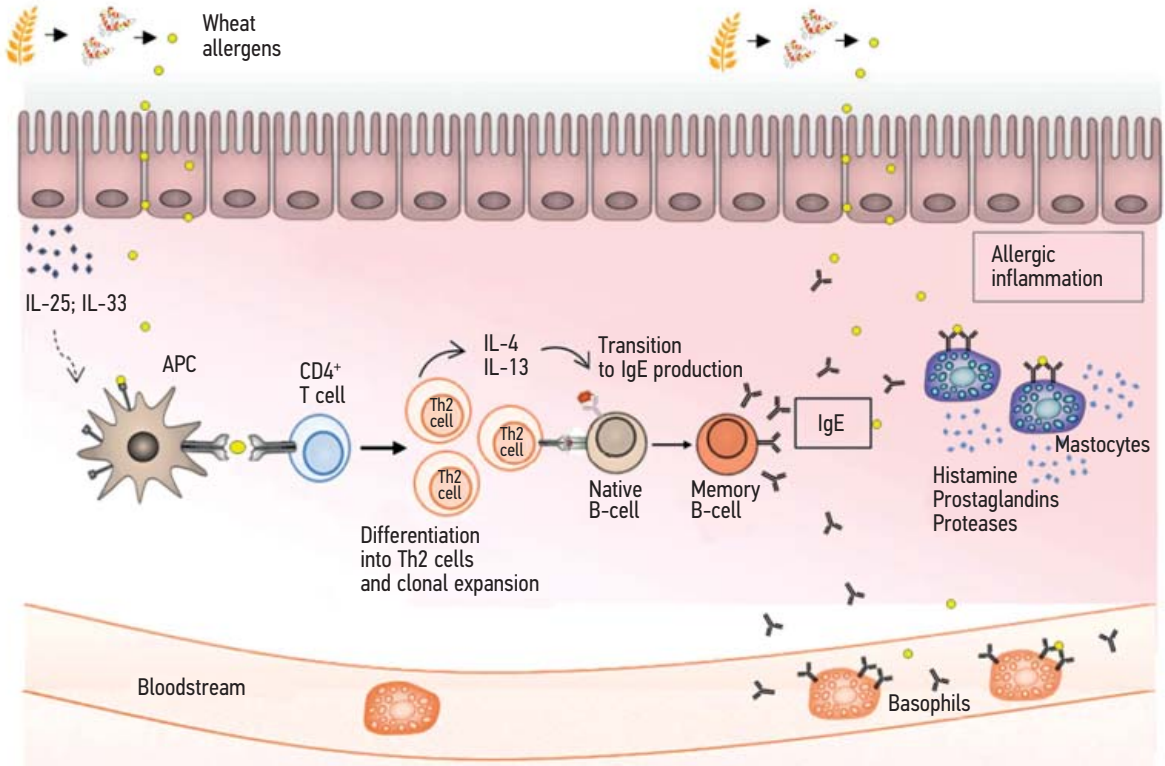

Fig. 2. Pathogenesis of wheat allergy. Wheat allergy can be triggered by several wheat proteins, named as allergens. Th2 cells play an essential role in the induction of IgE by B-cells in the initial phase of the allergic response. After a new consumption of allergen, IgE antibodies bound to their receptors on mast cells and basophils, recognize specific, which leads to consequent cell activation and release of inflammatory and vasoactive mediators. As a result, allergic inflammation is elicited.

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baker's asthma diagnosis, recognized as the gold standard, is based on the disease history, presence of specific IgE and/or positive results of scratch tests, and a positive bronchochallenge test [45]. Therefore, in most cases, the treatment of WA involves avoiding the intake of the allergen and refusing the physical load within 6 hours after consuming wheat-containing products during exercise-induced wheat anaphylaxis [45].

Another possible method is using several options for immunotherapy, where oral immunotherapy is the most studied. Therefore, following a study conducted in Japan that involved 18 pediatric patients with wheat anaphylaxis, a considerable decrease in the severity of clinical manifestations was achieved after two years of oral immunotherapy. Additionally, some children could consume more wheat without developing symptoms, the level of specific IgE decreased, and allergen tolerance was achieved in 60% of the participants [46]. The oral immunotherapy efficiency established in this study aligns with the results of the work of other studies; however, this method is not generally recognized due to the limitations in terms of sample size and the absence of a control group in the studies conducted [47, 48].

NON-CELIAC GLUTEN SENSITIVITY

The definition of non-celiac gluten sensitivity (NGS) is a subject of dispute in the scientific community due to the lack of understanding of the syndrome pathogenesis. Moreover, the role of other components of wheat, in addition to gluten, in the disease development is not excluded [49–51]. For example, the role of amylase and trypsin inhibitors, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are considered factors that contribute to the appearance of these clinical symptoms [52, 53] or trigger NGS in many patients [49, 54].

Additionally, NGS is usually combined with irritable bowel syndrome, resulting in difficulty in its diagnosis. Therefore, it is difficult to determine the exact prevalence of the disease, which varies from 0.16%–13% [4, 5]. Typically, NGS is known as a syndrome that comprises various intestinal and extraintestinal symptoms (Table 1) after the consumption of gluten-containing products in individuals without celiac disease or WA [55].

Despite the similar clinical presentation of WA and celiac disease, when examining individuals with NGS, neither specific IgE nor IgA to TG2 nor morphological changes in the characteristics of the small intestine due to celiac disease are detected [50].

Although no specific markers of NGS have been identified, the diagnostic criteria are the exclusion of celiac disease and WA, an objective improvement in well-being after refusal, or decreased gluten consumption. During an international meeting of experts on NGS in Salerno in 2014, it was proposed to use a double-blind, placebo-controlled cross-matching test with gluten as the gold standard for diagnostics when the patient receives two identical products where one contains gluten [55]. However, nowadays, method standardization is a challenge since it is necessary to achieve a complete identity of the taste of both products, which may be achieved in the coming years [56, 57].

POSSIBLE PATHOGENESIS OF NON-CELIAC GLUTEN SENSITIVITY

The immune system involvement in the development of NGS was initially questioned; however, numerous studies have indicated the predominant role of innate immunity without denying the role of acquired immunity. Therefore, during the study of intestinal biopsy samples, it was revealed that in NGS patients, the expression of Toll-like receptors (TLRs), which are involved in the reactions of innate immunity of types 1 and 2, is more pronounced than in healthy participants in the study. Contrary to celiac disease, in NGS, there is only a slight increase in the intraepithelial lymphocytes and a lower expression of cytokines characteristic of acquired immunity reactions [50]. Additionally, the HLA-DQ2 and HLA-DQ8 haplotypes characteristic of celiac disease are slightly more common in NGS than in the general population [50]. Given these data, an assumption arose about the predominant influence of innate immunity on NGS development. Figure 3 presents the proposed mechanism for NGS development.

Also, with gluten, as mentioned above, the influence of other components of cereals involved in the immune response activation is considered. Therefore, it has been shown that the amylase and trypsin inhibitors in wheat can activate dendritic cells by interacting with type 4 TLR and macrophages and monocytes [52, 58], potentially leading to the stimulation of innate immunity responses [52, 58]. Additionally, a gliadin derivative, a 33mer peptide, also interacts with TLR types 2 and 4, stimulating the production of pro-inflammatory cytokines and the development of the inflammatory process [59]. However, the inflammation severity and possible tissue damage are much lower than those in celiac disease and WA, resulting in a less pronounced clinical presentation [60].

Table 1. Symptoms of non-celiac gluten sensitivity

Groups of manifestations	Symptoms
Intestinal symptoms	Abdominal pain/discomfort, flatulence, diarrhea, alternating constipation, and diarrhea
Extraintestinal symptoms	Asthenia, headache, muscle and joint pain, skin rashes, depression, disturbances during sleep, etc.

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Treatment for NGS involves reducing or avoiding gluten-containing foods. There is evidence that this disease may be transient [49, 51, 55]. Therefore, after a period of gluten consumption restriction, an attempt to return these products gradually to the diet is possible [61]. Some NGS patients reported improved well-being following a FODMAP-restricted diet [53, 62]. Older wheat varieties were less immunogenic in gluten-associated diseases [63]. Patients with celiac disease must not consume even these variants of wheat; however, this may be an alternative to avoiding gluten in NGS [64].

Gluten-free diet adherence leads to the restricted intake of many essential macro-and micronutrients, which is not a healthy dietary option; therefore, it is recommended only after careful examination and detection of a gluten-associated disease [3, 49, 65, 66]. The denial of the existence of an NGS problem leads to uncontrolled self-medication and unreasonable adherence to a gluten-free diet. Furthermore, the ability to make an accurate diagnosis by a doctor and the correct selection of diet therapy will solve this problem.

CONCLUSION

Gluten-associated diseases have similar clinical manifestations, which develop in all cases after consuming gluten-containing products. Although the pathogenetic mechanisms underlying celiac disease and WA and practical treatment methods have been developed and well-studied, NGS remains a subject of discussion with no broad understanding of the processes underlying this disease, including a unified approach to its diagnosis and treatment. Despite the emerging assumption about the role of innate immunity in the pathogenesis of NGS, specific biomarkers have not yet been elucidated. Therefore, NGS is a diagnosis of exclusion, established in the absence of celiac disease or WA markers and improvement in well-being while following a gluten-free diet. NGS should also be confirmed with a double-blind, placebo-controlled cross-matching test with gluten, recognized as the gold standard for diagnostics. In the case of NGS, the role of gluten itself and other components of cereals, such as amylase and trypsin inhibitors, FODMAP, is not excluded.

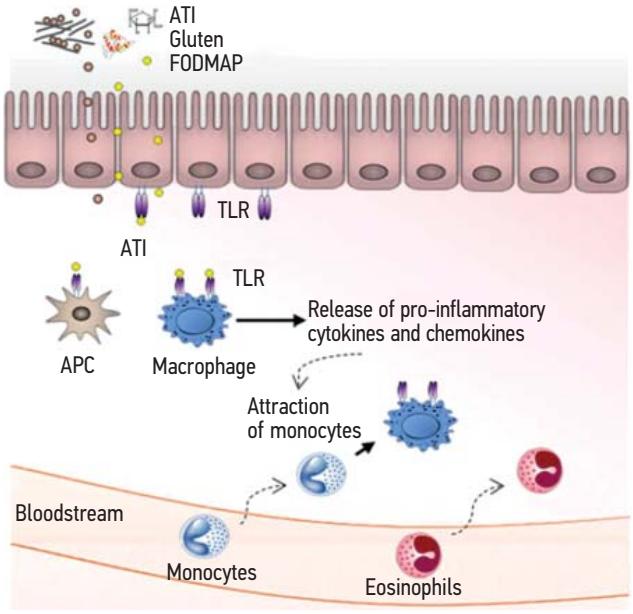

Fig. 3. Possible mechanism of nonceliac gluten sensitivity. The pathogenesis is expected to be based on innate immune responses due to the activation of TLR receptors of immune cells. In addition to the influence of gluten, amylase and trypsin inhibitors (ATIs), fermentable oligo-, mono-, disaccharides, polyols (FODMAPs) can also activate dendritic cells and macrophages through TLR4 and play a potential role in the development of non-celiac gluten sensitivity. This interaction results in the release of pro-inflammatory cytokines and chemokines, infiltration of tissues by eosinophils, but does not lead to damage to the intestinal mucosa. АПК — antigen presenting cells.

Therefore, further studies of the pathogenesis of NGS are required, including identifying specific markers of the disease for a more accurate diagnostic establishment and the correct treatment selection.

ADDITIONAL INFORMATION

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