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IgE-опосредованная пищевая аллергия и целиакия: обновлённый обзор

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АННОТАЦИЯ

Целиакия — хроническое аутоиммунное заболевание, которое поражает тонкий кишечник. У генетически предрасположенной категории людей это заболевание возникает при потреблении в пищу глютена — белка, содержащегося в пшенице, ячмене и ржи. Целиакия обычно проявляется у молодых пациентов детского возраста в виде нарушения всасывания питательных веществ, желудочно-кишечных симптомов и других осложнений, что связано с частичной или полной атрофией ворсинок проксимального отдела тонкого кишечника. С другой стороны, пищевая аллергия представляет собой аномальную иммунную реакцию на определённый пищевой белок, обуславливающую воспаление и ряд других симптомов от лёгкой крапивницы до жизнеугрожающей анафилаксии.

Несмотря на то, что механизмы, лежащие в основе целиакии и пищевой аллергии, различны, оба состояния включают иммунный ответ на пищевые белки. Текущее исследование показало, что возможность сосуществования IgE-А при целиакии и скрининге на пищевую аллергию следует рассматривать для людей с целиакией, особенно когда симптомы сохраняются даже после введения элиминационной диеты с исключением глютена. Однако связь между целиакией и пищевой аллергией до конца не понятна, и для изучения этой связи необходимы дополнительные исследования. Целью данного обзора является изучение доступной литературы о возникновении пищевой аллергии у пациентов с целиакией.

Ключевые слова: целиакия; пищевая аллергия; иммуноглобулин; IgE; физиопатология; обзор.

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IgE mediated food allergy and celiac disease: An updated review

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ABSTRACT

Celiac disease is a chronic autoimmune disorder that affects the small intestine. It is triggered in genetically predisposed individuals by consumption of gluten, a protein found in wheat, barley and rye. Celiac disease typically manifests in young pediatric patients as malabsorption of nutrients, gastrointestinal symptoms, and other health complications, which is associated with partial or total villous atrophy of the proximal small intestine. Food allergy, on the other hand, is an abnormal immune response to a specific food protein that causes inflammation and a range of symptoms, from mild hives to life-threatening anaphylaxis.

Although the mechanisms behind celiac disease and food allergy are different, both conditions involve an immune response to food proteins. The current study revealed the possibility of IgE-A coexistence in celiac disease and food allergy screening should be considered for people with celiac disease, especially when symptoms persist even after implementing a gluten-free. However, the relationship between celiac disease and food allergy is not fully understood, and more research is needed to explore this link.

This review aims to examine the available literature for the occurrence of food allergy in subjects with celiac disease.

Keywords: celiac disease; food allergy; immunoglobulin; IgE; physiopathology; review.

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INTRODUCTION

Celiac disease (CD), defined as a gluten-induced enteropathy in genetically predisposed individuals [1], has been the subject of undisputed renewed interest in recent years and has been the focus of several studies since it was first described by Samuel Gee in 1888. It affects approximately 1.4% of the population, and its incidence varies geographically and appears to be increasing over time in several countries [2,3]. It is characterized by villous atrophy of the small intestine caused by the absorption of gluten proteins contained in wheat (gliadin), barley (hordein), and rye (secalin) [4]. CD typically manifests in young pediatric patients as gastrointestinal and malabsorption symptoms. The nonclassical form of CD encompasses symptoms outside the gastrointestinal tract, including slowed growth, anemia, neuropathy, chronic fatigue, and headaches [5].

Generally, the treatment of CD consists of a lifelong gluten-free diet (GFD) based on naturally gluten-free foods and labeled gluten-free products [6]. Despite this diet, gastrointestinal symptoms may persist, either because of the implicit ingestion of gluten or because of other factors that have not yet been identified [7]. Indeed, a study conducted in Poland showed that the symptoms of Polish patients with CD persisted for up to 6 years after the adoption of a balanced GFD. One of the potential causes of this persistence could be the concomitant presence of other diseases. In a recent study, participants most frequently mentioned anemia (34%) and allergies (13%) when asked about associated comorbidities [8]. Moreover, patients with CD have a fundamentally sensitive immune system that could cause damage, which not only limits their ability to absorb nutrients but also exposes them to an increased risk of potentially serious health problems, including sensitization of their intestines to different foods and inflammation in response to certain foods [9].

Unlike the deregulated immune response seen in autoimmune diseases, where the immune system attacks its cells, allergy results from an exaggerated immune response against external proteins, leading to allergic inflammation [10]. Many recent publications have confirmed an association between allergy and autoimmunity. This suggests that those who suffer from autoimmune disease may be at a greater risk of developing other immunological diseases, namely, allergic inflammation [11,12,13]. Indeed, some studies have indicated that patients with CD tend to have allergic manifestations more frequently than the general population [14]. CD and food allergy (FA) share a common feature, consisting of dysfunction of the immune system, particularly the regulatory T cells present in the gastrointestinal tract [15]. In both cases, treatment is often based on the adoption of a specific dietary elimination diet. However, the precise relationship between CD and FA remains unclear and requires further research. To date, no in-depth study of FA prevalence in large numbers of children with CD has been conducted.

In this review, we aimed to examine the etiology and epidemiological pathogenesis of CD and FA in children and discuss their association. We also sought to understand the persistence of clinical symptoms of CD despite the adoption of a GFD.

CELIAC DISEASE

Definition and prevalence

CD, also known as gluten-sensitive enteropathy or celiac sprue, is a chronic enteropathy of the small intestine caused by a gluten-mediated immune reaction in genetically susceptible individuals [16]. It is caused by the absorption of the storage proteins found in certain grains, including gliadins in wheat, hordeins in barley, and scalin in rye; however, no consensus has been reached regarding the potential toxicity of oat avenins [17]. CD typically manifests as a malabsorption syndrome that affects both clinical and biological aspects and is associated with partial or total villous atrophy of the proximal small intestine [18]. Generally, CD symptoms vary from one person to another but are often related to the digestive system. Common signs of CD include vomiting, bloating, nausea, abdominal pain, diarrhea, and constipation. However, it may also present with non-gastrointestinal abnormalities such as chronic fatigue, headaches, anemia, and delayed growth and development [19].

Although CD occurs worldwide, it is most prevalent in northwestern Europe, where its incidence is high compared with that in other regions [2]. Its global prevalence varies considerably from population to population, with a global estimate of 1.4% (95% confidence interval, 1.1%–1.7%) [2]. In recent years, an increase in its frequency has been observed, doubling its prevalence in the last 20 years [20]. Recent data suggest that the incidence and prevalence of CD are increasing in the pediatric population [3,21,22].

Diagnosis and pathophysiological hypothesis

CD is often underdiagnosed because of the variable clinical presentation. Signs and symptoms can vary greatly from person to person, which can make diagnosis difficult [23]. To diagnose CD, healthcare professionals typically use several approaches, including clinical examination, history taking (medical history), human leukocyte antigen (HLA) testing, histopathology (small intestine biopsy), and serology (blood tests) [24].

In 2012, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition published guidelines that allowed for a diagnosis based on serology, without the routine need for histopathology in some cases [23]. In suspected CD, regardless of the child's age and presence or absence of symptoms, an initial test for antitransglutaminase antibodies ATG type IgA with total IgA assay is currently recommended. Moreover, it is first necessary to check that the child consumes sufficient quantities (at least 5 g) of

gluten regularly. If the TGA-IgA is 10 times the upper limit of normal (ULN), CD can be diagnosed without a biopsy as long as the second blood sample is positive for immunoglobulin A endomysial antibodies (EMA-IgA). This second sample is essential because IgA EMA is highly specific and helps eliminate false positives by confirming celiac autoimmunity. However, if the TGA-IgA is <10 times the ULN, biopsies of the distal duodenum and bulb should be performed [25]. The determination of HLA DQ2/DQ8 antigens is useful in the diagnosis of CD but is not considered a mandatory criterion for diagnosis [23].

The *HLA-DQ2* (95%) and *HLA-DQ8* (5%) genes are associated with an increased risk of developing CD [26]. However, many people with these genes do not develop CD, suggesting that other factors are also involved. In addition, gluten consumption, particularly in genetically susceptible individuals, is considered a key trigger for CD. Other environmental factors, such as infections, gut microbiota, and dietary habits, may also contribute to CD development [27] (Fig. 1).

Recent studies have also highlighted the involvement of innate immunity in CD development. Specifically, gliadin was proposed to stimulate the innate immune response in the intestine [28]. This stimulation is facilitated by the action of the enzyme tissue transglutaminase, which causes the deamidation of gliadin, forming negatively charged gliadin peptides. These peptides have a high affinity for the major histocompatibility complex class II (HLA-DQ) expressed on the surface of antigen-presenting cells. These cells are recognized by CD4+ T lymphocytes in the intestine, leading to their activation and the production of proinflammatory cytokines, notably interleukin (IL-15). This immune reaction destroys intestinal mucosal cells, resulting in the villous atrophy characteristic of CD [25] (Fig. 2).

Individuals with untreated CD may have altered intestinal permeability, which results in the increased passage of food antigens through the intestinal lining and can trigger food-related hypersensitivity reactions [14]. Indeed, the CD-associated chronic increase in intestinal permeability allows food antigens to pass through the intestinal mucosa and come into contact with cells of the immune system; this phenomenon is called translocation. Indeed, studies have shown that exogenous peptides from the diet can share amino acid motifs with self-tissue peptides presented by HLA molecules on antigen-presenting cells. This similarity can lead to cross-reactivity by immunological mimicry, which disrupts immune tolerance in genetically predisposed individuals [29].

Through this mechanism, the involvement of innate immunity in CD can be deduced as a promising avenue of research to better understand the mechanisms of the disease and develop primary prevention and therapeutic strategies. In 2016, scientific authorities such as the Committee on Nutrition of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and European Food Safety Authority

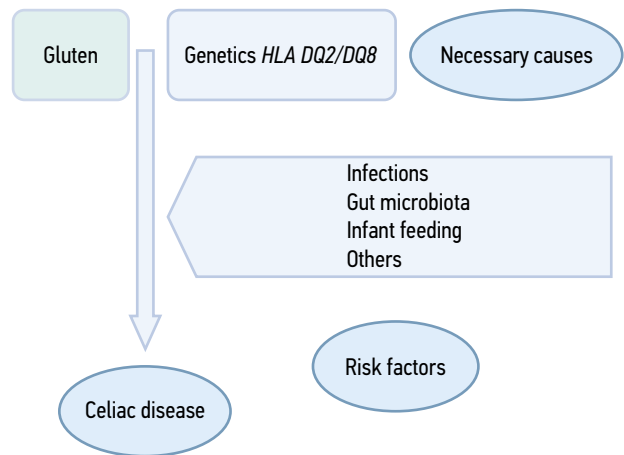


Fig. 1. Causes of celiac disease.

recommended that gluten should be introduced into the diet of infants aged 4–12 months. No specific directives have been issued concerning the type of gluten to be used when introducing gluten. On the basis of limited data, excessive gluten consumption should be avoided in the first few months after gluten introduction. However, further research is required to establish more precise recommendations in this area [30].

Generally, the treatment for CD is lifelong GFD. This is the only effective and currently available treatment for CD [31]. It is based on a very restrictive but necessary exclusion of all foods containing one of the three toxic grains (wheat, barley, and rye) to prevent complications, particularly naturally gluten-free foods (N-GFF) and labeled gluten-free products (L-GFP) [32]. This diet involves interrupting gluten-specific LTCD4+ activation and IL-15 production. This blocks the activation of intraepithelial lymphocytes in the intestine and the destruction of the epithelium, allowing them to be reconstituted from the stem cells present in the intestinal mucosa [33]. Adherence to GFD is assessed by the improvement of clinical (very rapid) and biological signs: antitransglutaminase antibodies decrease and then disappear after 6–12 months of a well-followed GFD [33]. Unfortunately, strict adherence to a GFD entails significant lifestyle changes that can affect the quality of life of people with CD. Many children with CD may feel different or stigmatized when they have to consume GFF, and this special diet can have negative social consequences, which can alter their quality of life. In addition, the constant concern about cross-contamination, particularly with N-GFF, is another factor that can reduce quality of life [34].

FOOD ALLERGY

Prevalence

The World Health Organization ranks allergic diseases as the fourth most common chronic disease worldwide. According to the 2011 report of the World Allergy Organization (WAO), 30%–40% of the world's population is affected by one

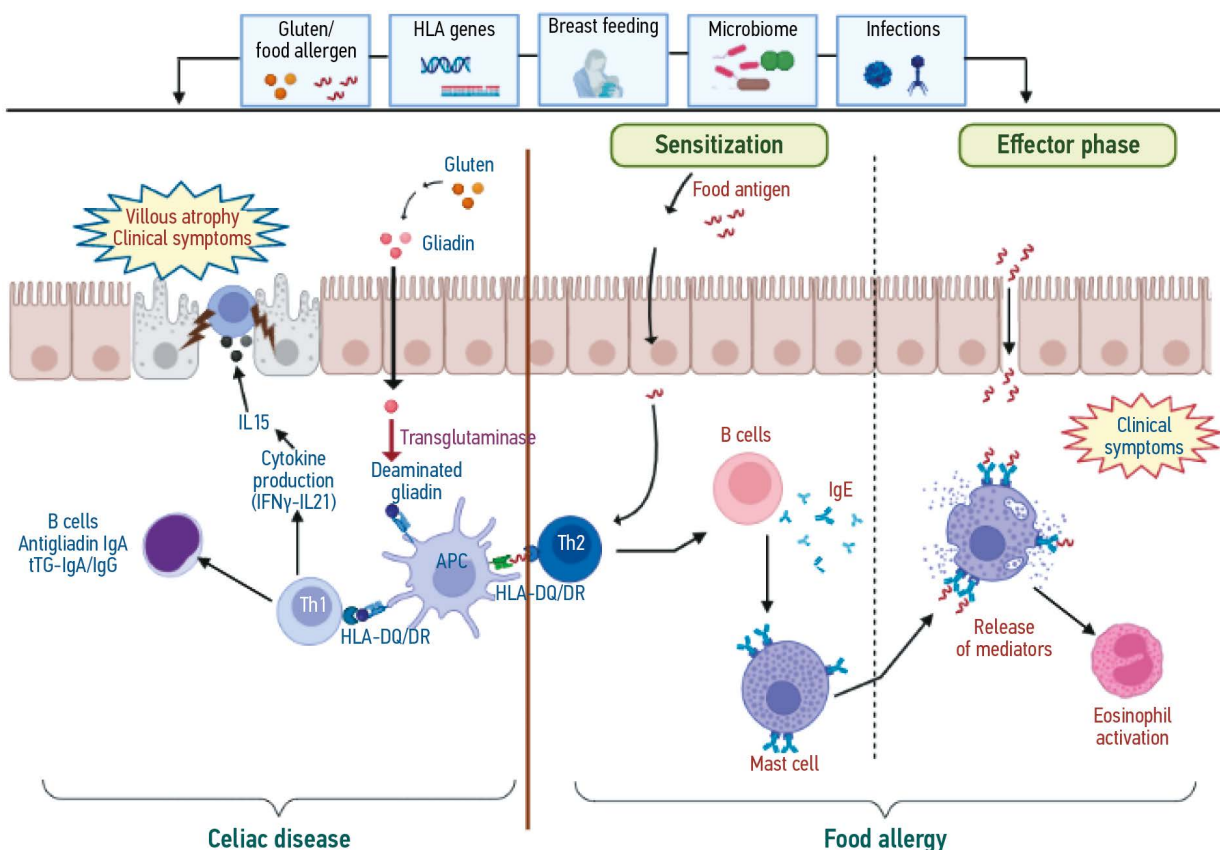


Fig. 2. IgE-dependent food allergy and celiac disease: Immunological mechanisms, genetic and environmental factors. IgE — immunoglobulin E; APC — antigen-presenting cell; IL15 — interleukin 15; IL21 — interleukin 21; IFN γ — interferon gamma; tTG-IgA — tissue transglutaminase IgA; HLA — human leukocyte antigen. (Illustrated by BioRender software).

or more allergic diseases [35]. In the food field, it remains a concern, particularly in children affected nearly three times more than adults [36]. In Europe, FAs are increasingly reported. The point prevalence of sensitization based on specific IgE was 16.6% (95% CI 12.3–20.8) [37].

The epidemiology of FAs has become a subject of great interest because accurate data are essential to assess allergic risks and serve as a basis for food safety policies, in terms of both actions within the major food industries and regulations [38]. Worldwide, the most incriminating food allergens in children (responsible for nearly 90% of FA cases) are chicken egg, cow’s milk, fish, shellfish, peanut, soy, wheat, and hazelnut, with considerable differences from country to country [39].

Definitions and clinic

FA is an immune system response to certain food proteins. It is very distinct from food intolerances, which are defined as non-immune reactions that involve enzymatic, pharmacological, toxic, or metabolic mechanisms. Generally, FAs can be divided into non-IgE-dependent allergies and IgE-mediated FAs [40].

Non-IgE-dependent FAs, also known as delayed FAs, are characterized by symptoms that develop within several hours to several days after the ingestion of the trigger food. By contrast, IgE-mediated reactions are generally rapid in

onset, and clinical symptoms develop within minutes to hours after ingestion. They are also called immediate FA [41] (Fig. 3).

Most commonly, allergic reactions can cause symptoms in several organs, such as the skin, respiratory tract, and gastrointestinal tract [36]. Atopic dermatitis is the main manifestation of FA in children. Other cutaneous signs include acute urticaria and angioedema. Digestive disorders such as vomiting, abdominal pain, nausea, diarrhea, and rectal bleeding in infants are the most common. Asthma can be also a manifestation of FA; however, it is often associated with other signs, such as urticaria or angioedema [39].

Pathogenesis

FA is influenced by genetic and environmental factors [42]. Some studies have shown that the genetic predisposition to FA is modulated by epigenetic mechanisms, such as DNA methylation, which can be influenced by environmental factors such as nutrition and microbiota [11]. Indeed, Amat and Houdouin suggested that changes in the gut microbiota composition, such as decreased microbial diversity or increased prevalence of certain bacteria, may play a role in FA susceptibility. These changes can affect the immune system, leading to increased reactivity to food allergens [43]. Studies have also shown that diet in early childhood can have a significant effect on the risk of FA development.

In this regard, The American Academy of Pediatrics has recommended delaying the introduction of allergenic foods, such as cow's milk, in infants who are at a higher risk of developing allergy until 1 year of age and seafood or peanuts until age 3 [44].

Pathophysiologically, the allergen is captured and processed by antigen-presenting cells, which then present it to Th2 lymphocytes. The latter activate B cells, which produce allergen-specific IgE antibodies. These antibodies then bind to receptors on the mast cells of the person with allergy. This is the sensitization phase [41]. When the person is exposed to the allergen again, it binds to IgE antibodies attached to mast cells, which triggers a cascade of biochemical reactions within these cells. This releases substances such as histamine, which causes allergic symptoms [41] (Fig. 2).

Therefore, allergic inflammation is, in principle, a Th2 cell- and IgE-dependent process [45]. They appear to play a very crucial role in FA. As a result, pharmacological and genetic inhibition of calcium channels, including voltage-gated channels (Cav1) that are considered of primary importance for calcium entry into Th2 cells, significantly reduces cytokine expression in Th2 cells [46]. Furthermore, studies have shown that IL-15 plays an important role in the activation of allergen-specific Th2 T cells and stimulation of allergic inflammation *in vivo*. Rückert et al. [47] revealed that the inhibition of endogenous IL-15 with soluble IL-15R α during the sensitization phase prevents the development of antigen-specific Th2 cells, resulting in a marked reduction in the production of specific IgE and IgG and induction of allergic inflammation.

CELIAC DISEASE AND FOOD ALLERGY

The relationship between CD and allergies is not yet fully understood; however, some studies have indicated that patients with CD tend to have allergic manifestations more frequently than the general population [14]. Both CD and FA are immunological diseases. They develop in a predisposing genetic background but involve complex interactions between immune and environmental factors [20,40] (Figs. 4, 5).

In theory, CD is considered a diarrheal disease. Although gluten ingestion and resulting small intestine inflammation are possible causes of chronic diarrhea in patients with CD after diagnosis, other epidemiologically related conditions can cause diarrhea [48]. Typically, the treatment for CD is a lifelong GFD. Despite this diet, gastrointestinal symptoms may persist either because of implicit gluten ingestion or because of other factors to be identified. Indeed, Guennoui et al. [6] showed a high prevalence of gluten contamination affecting both N-GFF and L-GFP, which was estimated at 15.12% (95% CI, 9.56%–21.70%), with >20 mg/kg of gluten. N-GFF were significantly more contaminated than L-GFP and than meals in food services (28.32%, 9.52%, and 4.66%, respectively, $p < 0.001$). These results explain the failure of the GFD [49]. On the contrary, this lack of effect of the diet is most

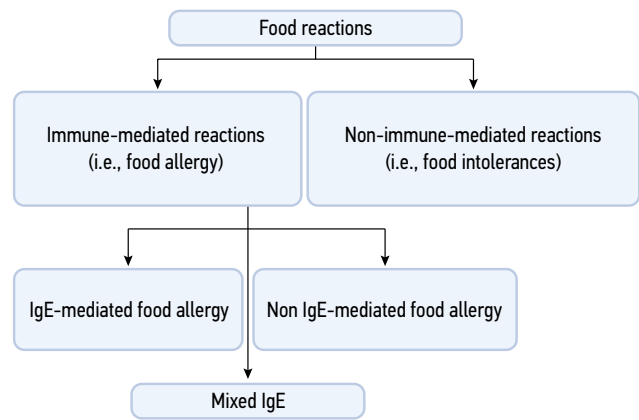


Fig. 3. Classification of food reactions. IgE — immunoglobulin E.

likely related to insufficient follow-up of <12 months [14].

From another view, the diet prescribed to patients with CD did not improve the clinical and biological symptoms of their pathology following FA. Indeed, a study from Poland found that symptoms in patients with CD persisted for up to 6 years after the introduction of a GFD. According to this study, one of the possible causes of the persistence of these symptoms may be the coexistence of other diseases, particularly allergies, at 13% [7,8]. In the same sense, Syrigou et al. [50] documented a case involving a girl suffering from both CD and soy allergy. The identification of the soy allergy was critical for the proper management of CD because the patient had been experiencing persistent gastrointestinal symptoms and villous atrophy, even after strictly adhering to a GFD for at least 6–12 months. They concluded that the diagnosis of this coexisting FA is important for the effective treatment of CD. This applies not only to soy but also to other food allergens, which must be excluded from the diets of individuals with CD to reduce the gastrointestinal symptoms that persist in such patients [50]. Similarly, Fine et al. [51] documented the cases of 24 people with CD who continued to suffer from persistent diarrhea despite a GFD for more than a year. However, after eliminating cow's milk and foods that tested positive on skin tests, 22 of the 24 patients had resolved symptoms within 3 weeks.

Furthermore, after reviewing the literature on the presence of A-IgE in individuals with CD, an alternative hypothesis to consider is that patients with CD may be sensitized to wheat. The adoption of a more diversified diet could lead to a decrease in wheat tolerance and, consequently, favor the development of wheat allergy [52]. Indeed, Sarah et al. [53] reported that some patients with CD on a GFD developed wheat allergy following accidental exposure to wheat. Traces of cereals present in GFF act as a sensitizing factor in patients with CD, and patients with persistent symptoms, despite a GFD, likely manifest symptoms related to wheat allergy rather than CD. Therefore, this issue needs further investigation because wheat avoidance in patients with CD and wheat allergy may lead to fatal anaphylaxis [54]. Similarly, cow's milk protein allergy is a well-known cause of enteropathy, particularly in

children. A recent case study conducted by Merikas et al. [55] reported the case of a young patient with CD who presented with persistent elevation of ATG despite a GFD follow-up. After developing milk-related symptoms and a positive skin test result for milk allergy, the patient decided to eliminate milk proteins from her diet. For the first time, her ATG level normalized after the elimination of cow's milk.

Therefore, a diagnosis of CD does not necessarily rule out the possibility of FA. Children with CD may experience gastrointestinal symptoms that stem from both CD and FA. Consequently, regardless of age, children with CD must be assessed for the presence of additional FA.

Despite the strong interest in the association between FA and CD, very few studies are available. The first publication that addressed the frequency of allergy in children with CD was published in 2021 by Beata Cudowska et al. This single-center study found that >20% of children with CD had confirmed IgE-mediated sensitization. Seven of these children (58.3%) were found to have food sensitization. In addition, half of the patients had sensitization to more than one food allergen, whereas some also had coexisting sensitization to airborne allergens (pneumallergens) [10]. Similarly, another study conducted in Italy showed a significant association between CD and FA, revealing that the prevalence of CD in children with severe allergy is 4–5 times higher than that in the general population and patients with mild allergy. Hypothetically, patients with untreated CD may experience an increase in food-dependent hypersensitivity because of the changed permeability of their intestinal mucosa, resulting in a greater flow of food antigens through the mucosa. Conversely, in some patients with allergy, altered intestinal permeability has been observed, which could break gluten tolerance and lead to CD development in individuals with a genetic predisposition [14]. Another study stated that CD is very common in patients with allergy and could affect the severity of FA. Indeed, severe FA was observed in 12 patients with FA + CD (80%, according to Lega et al., screening for CD should be considered in patients with severe or persistent FA [56].

In children, FA, particularly IgE-mediated forms, is a significant public health issue with allergic reactions ranging in severity from gastrointestinal disorders and skin irritation to anaphylaxis, anaphylactic shock, and death. Park et al. [57] highlighted the presence of multiple FAs in children that are often not accounted for in prevalence studies. They showed that >70% of children with FA are either allergic or have to abstain from 3–4 foods. They suggest that cases with multiple FAs constitute a sizable fraction of the FA population. These children often show growth delay compared with children

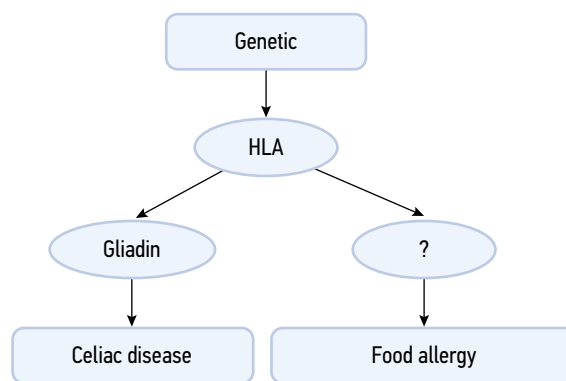


Fig. 4. Diagram illustrating the role of genetics in food allergy and celiac disease. HLA — human leukocyte antigen.

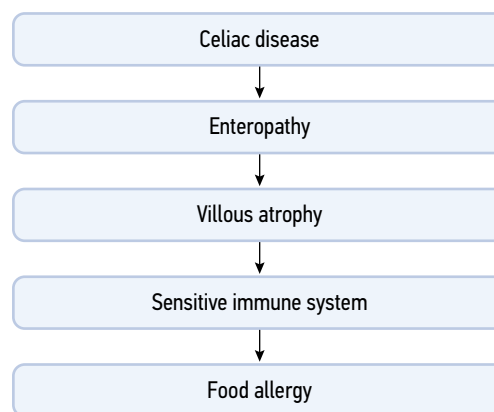


Fig. 5. Diagram illustrating the pathophysiological sequence from celiac disease to food allergy.

with simple FA [58]. Faced with this situation, early diagnosis is essential to institute an eviction diet, which remains the only effective treatment to avoid symptom recurrence.

Unfortunately, too strict diet avoidance does not promote recovery and can have harmful effects (affects growth and quality of life and calcium and vitamin deficiency). The help of a dietician and a psychologist can be quite essential in the management of these patients, and new prevention strategies should be applied to children at risk of developing FAs. Moreover, proactive actions are necessary to minimize the presence of gluten and ensure that appropriate precautions are taken to meet the dietary needs of people with CD, regardless of economic constraints.

CONCLUSION

This study revealed the possibility of IgE-A coexistence in CD. However, further research is needed to confirm the association between CD and FAs. This emphasizes the importance of monitoring individual health and taking steps to reduce exposure to potential allergic triggers.

ADDITIONAL INFORMATION

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version to be published and agree to be accountable for all aspects of the work. Hasna Ait Said — drafted the paper and designed the figures; Lahcen Elmoumou and Nadia El Kadmiri — designed the protocol; Bouchra Rherissi and Morad Guennouni — revised the manuscript.

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