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Review article

Wheat allergy

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Introduction

Food allergy is a growing health problem which emerged as the "second wave" of the allergy epidemic, lagging decades behind the 'first wave' of asthma, allergic rhinitis and inhalant sensitization.[1] Data on challenge-diagnosed FA in some countries (e.g. China and Africa) show rising rates that became similar to those in Western countries.[2] A report from US Centers for Disease Control and Prevention (CDC) indicated that among children aged 0–17 years, the prevalence of food allergies increased from 3.4% in 1997–1999 to 5.1% in 2009–2011, a 50% rise.[3] About 6% of children experience food allergic reactions in the first three years of life, including approximately 2.5% with cow's milk allergy, 1.5% with egg allergy, and 1% with peanut allergy.[4] Wheat is one of the five most common foods that trigger allergic reactions in children.[5]

Epidemiology of Wheat Allergy

IgE-mediated wheat allergy (WA) in children is one of the most frequent food allergies in Westernized countries, affecting between 0.4 and 1% of children.[6] The prevalence of WA varies depending on the diagnostic methods used and the ethnicities studied.[7] In Asia, highest prevalence of WA was found in Japan and Korea, with far lower rates of prevalence observed in other Asian countries.[8] In a major teaching hospital in Thailand, it was found that among children less than 3 years of age, the most common food with positive challenge was wheat (70%) whereas among children 3 years of age or older, shellfish, as a cause of FA, prevailed (42%).[5] In Germany and Finland, it has been reported as the third most common allergen, after milk and egg.[9] In Brazil, wheat sensitization was as high as 20% in allergic children versus 8.1% in healthy controls.[10] Taking into account all gluten-related disorders, it has been estimated that about 3% of the human population suffer from wheat intolerance (1% WA, 1% celiac disease, 1% non-celiac gluten sensitivity).[11]

Wheat grain proteins:

Triticum aestivum (bread wheat) is the most widely grown crop worldwide being easy to grow in different climates and delivering high yields.[12] All of the wheat-induced diseases are caused by wheat proteins which constitute 10%–18% of the grain mass, depending on the strain. The main component (70%) of the wheat grain is starch. Depending on their dissolving agent, the wheat grain proteins are categorized into four main fractions: albumins (15%), globulins (7%), gliadins (33%), and glutenins (45%). Albumins are soluble in water; globulins, in salt solutions; gliadins, in alcohol; and glutenins, in dilute acid and alkali. Albumins and globulins are structural proteins that contain many enzymes. Gliadins and glutenins are referred to as gluten. They are storage proteins.[7] WA is highly cross-reacting with other cereals; mainly rye and barley.[13]

Some wheat protein components were intensely studied for the diagnosis of WA: glutenins with low and high molecular weight (LMW-glutenins and HMW-glutenins); alpha, beta, gamma and delta gliadins, as well as non-specific lipid transport protein Tri-a14. However, none proved to have high specificity and sensitivity and, therefore, the precise diagnosis still relies on standardized challenges.[14]

The Spectrum of Wheat Sensitivity

Wheat sensitivity comprises WA (induced by gluten and other wheat components) and other gluten related disorders (GRD).[15] The term GRD is the overarching term proposed by an international, multidisciplinary task force, the Oslo group, to describe all gluten triggered diseases. GRD include coeliac disease (CD), nonceliac gluten sensitivity (NCGS), dermatitis herpetiformis (DH), and gluten ataxia.[16] **(Figure 1)**

CD occurs in genetically susceptible individuals with HLA-DQ2 and/or HLA-DQ8 genotypes and has a characteristic serological profile (such as anti-tissue transglutaminase (tTG) IgA, anti-endomysium IgA (EMA) and anti-deamidated gliadin peptides IgG (DPG).[15] Gliadin peptides activate T-lymphocytes in the lamina propria,

producing proinflammatory cytokines, inducing either a T-helper 1 response dominated by IFN-γ, or a T-helper 2 response inciting clonal expansion of B-lymphocytes.[17]

The NCGS is widely accepted as being distinct from CD, but it remains a diagnosis of exclusion.[15] As objective diagnostic data and specific biomarkers are lacking, response to a gluten-free/wheat-free diet can confirm the presence of NCGS.[18] From an allergist perspective, the existence and the possible triggers of NCGS are controversial.[19]

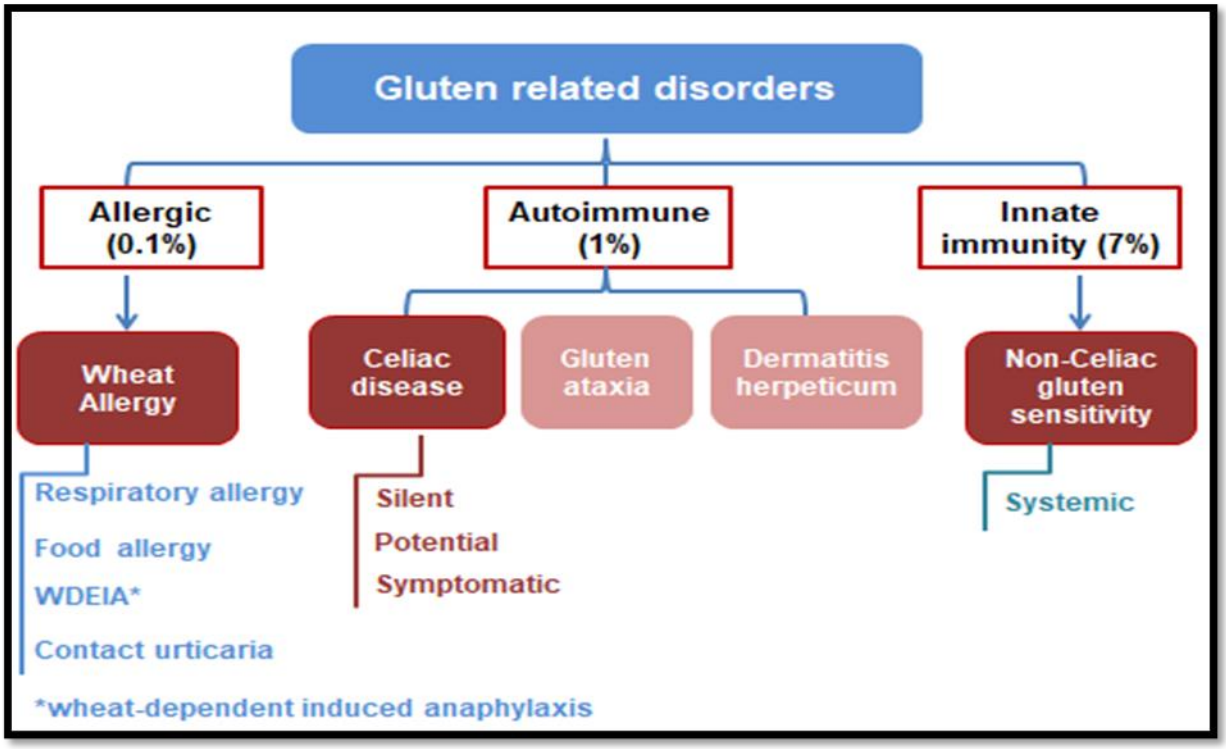

Figure 1. Classification of gluten-related disorders (Quoted from Lammers et al.[20]).

Mechanism of Wheat Allergy

The suggested mechanism of genesis of WA is shown in **figure 2.** WA, classified as a classic FA, is both IgE and non-IgE mediated (**Figure 3**) **IgE mediated reactions** are a consequence of Th2-biased immune dysregulation with production of IL-4, IL-5, and IL-13 and induce B-cell allergen specific IgE production. **Non-IgE mediated reactions** are induced via a Th2 lymphocytic response independent from IgE-specific antibodies to wheat and are characterized by an eosinophilic infiltration inducing tissue inflammation, which is exacerbated by type 2 innate lymphoid cells (ILC2) action.[21]

Thymic stromal lymphopoietin produced by the dysfunctional esophageal epithelium in genetically predisposed individuals could be one of the major initial drivers of the Th2 inflammation in eosinophilic esophagitis (EoE).[22]

Clinical Picture of Wheat Allergy

WA prevails chiefly in children with a family history of atopy.

In IgE-mediated wheat allergy, commonly, symptoms develop within minutes to 1–2 h after the ingestion of wheat. A cross-sectional study among Thai children who presented with IgE-mediated wheat allergy during 2001 to 2015 revealed that WA presented very early in life at a median age of 7 months and that the vast majority (90%) developed their first reaction after their first ingestion of wheat.[25] Almost all of children with WA are diagnosed with allergies to other foods and other allergic disorders, most commonly AD (78%–87%). Half of patients suffer from asthma (48%–67%) and/or AR (34%–62%).[26] In young children gastroenterological symptoms prevail, such as vomiting, diarrhea or, rarely, abdomen pains. In about 40% of children skin symptoms are observed in a form of urticaria, erythema, angioedema, pruritus, or worsening AD.[27] Intestinal symptoms reduce with age; therefore, older children suffer

mostly from dermatitis, which is sometimes accompanied by respiratory disorders (wheeze, stridor, persistent cough, hoarse voice, respiratory distress) and, in the most severe cases, anaphylaxis.[28] Wheat has been increasingly reported to be a risk factor for severe anaphylaxis as well as ***wheat-dependent, exercise-induced anaphylaxis (WDEIA)*.** In a population of children allergic to wheat, more than 50% had experienced anaphylaxis upon wheat ingestion.[29]

Non-IgE mediated WA is characterized by reactions occurring between 2-48 hours of longer after exposure. Wheat has been found to be an important trigger of EoE and eosinophilic gastritis (EG).[22]

Oral mite anaphylaxis (OMA) or the pancake syndrome is an allergic reaction occurring shortly after ingestion of foods made with mite-contaminated flour (first reported with pancakes, hence came the name) where heat resistant mite allergens are preserved during the short cooking time. It has also been described after eating bread, pasta, pizza, corn, oats, and white sauce or other meals made with mite-contaminated flour. Fatal cases of OMA have been reported highlighting its importance as a cause of anaphylaxis. It is often confused with wheat or other allergies, which can lead to misdiagnosis.[30] A recent study has highlighted the possibility of OMA happening in childhood and, in some occasions; it simulates acute asthma in its presentation.[31]

Baker's asthma is one of the most common occupational asthma caused by inhalation of wheat flour. Diagnosis rests on occupational history, evidence of IgE sensitization to wheat and specific inhalation challenge tests.[32]

Diagnosis of Wheat Allergy

As any FA, a careful **clinical assessment** is fundamental to the diagnosis of WA. History taking and physical examination can establish the likelihood of the diagnosis, suggest whether the mechanism is an IgE or non-IgE mediated one, and provide a guide to appropriately select and interpret further investigations. Medical history should ascertain the form of wheat (raw, cooked or baked), the route of exposure (oral, inhalation, or skin contact), the time lapse between exposure and development of symptoms, whether this link between symptoms and the incriminated food has been noticed on other occasions, and whether a temporal relation exists with exercise or alcohol ingestion.[33] WA diagnosis is difficult because not all of the major wheat grain allergens are recognized.[7]

Skin prick test (SPT) to wheat flour:

Generally, a commercial wheat extract is used, the specificity of which is very low. Some allergologists prepare an in-house wheat flour solution, but its specificity is also very low.[33]

Wheat specific IgE (sIgE):

Determination of serum concentrations of specific IgE to whole wheat extract can be used but their specificity is low despite high sensitivity.[34] In a retrospective study evaluating the performance of wheat and ω-5 gliadin sIgE in the face of the results of oral food challenge (OFC) in children, a cutoff of 2.88 kU_A/L had a sensitivity of 95%, whereas a cutoff of 78.1 kU_A/L had a specificity of 95%. Considering both sensitivity and specificity, a cutoff point for wheat sIgE as high as 12 kU_A/L, gave a specificity of 70% and a sensitivity of 66.67%[22]**.** Hence, it has been deduced that OFC is important to confirm the diagnosis even in patients with high wheat sIgE, to avoid false mislabeling of these patients as wheat allergic.[35]

OFC: is usually performed in its open form, as the majority of the observed adverse reactions are of the objective nature. The patient is given whole wheat starting from small doses of wheat-specific protein (1–50 mg) followed by increasingly larger hourly doses ending with a cumulative dose of up to 0.5–1 g of wheat protein.[28]

Management of Wheat Allergy

At the moment, management of IgE mediated WA is mainly based on avoiding both food and inhaled wheat allergens. Patients with WA must be trained to identify relevant food allergens in the labels, and written instruction should be given to effectively eliminate wheat from their diet. In case of accidental exposure and anaphylactic reaction, epinephrine administration with a self-injector device is the lifesaving treatment. This comes in strengths of either 0.15 or 0.3 mg and is injected into the vastus lateralis muscle (mid lateral thigh). The dose may be repeated at intervals of at least 5 minutes if necessary.[34] Unfortunately, this device is barely available in Egypt, expensive and is not covered by medical insurance.

Clinical trials for oral immunotherapy (OIT) so far are extremely heterogeneous and therefore their results are not comparable. Differences encompass dosage, amount and frequency, duration of build-up and maintenance phases, type of allergen used, patient characteristics, recording adverse events, and adjuvant therapies.[36]

Is Wheat Allergy Preventable?

It has been recommended to introduce foods containing strong allergens into the infants' diets as early as between the 17th and 26th weeks of life. In a study by Poole and coworkers,[37] a total of 1612 children were enrolled at birth and followed to a mean age of 4.7 years. Children who were first exposed to cereals after 6 months of age had an increased risk of wheat allergy compared to those whose first encounter with cereals was at an earlier age. In a systematic review, early introduction of gluten was associated with a reduced risk of wheat sensitisation up to 5 years in one observational study (n = 3781) but not in RCTs (n = 1303). In addition, the effect of breast feeding on WA development was inconclusive.[3].

Natural History of Wheat Allergy

Few data are available regarding the natural history of wheat allergy. A food challenge-based study conducted on 103 patents with wheat-induced symptoms and a positive wheat IgE test result, resolution occurred at a rate of 29% by 4 years, 56% by 8 years, and 65% by 12 years.[39] The median age of tolerance from wheat allergy was reported to be approximately 6 years of age; however, a minority will have wheat allergy persisting into adolescence and adulthood[40]. The higher the wheat IgE levels, the older a child was when they developed tolerance to wheat.[36]

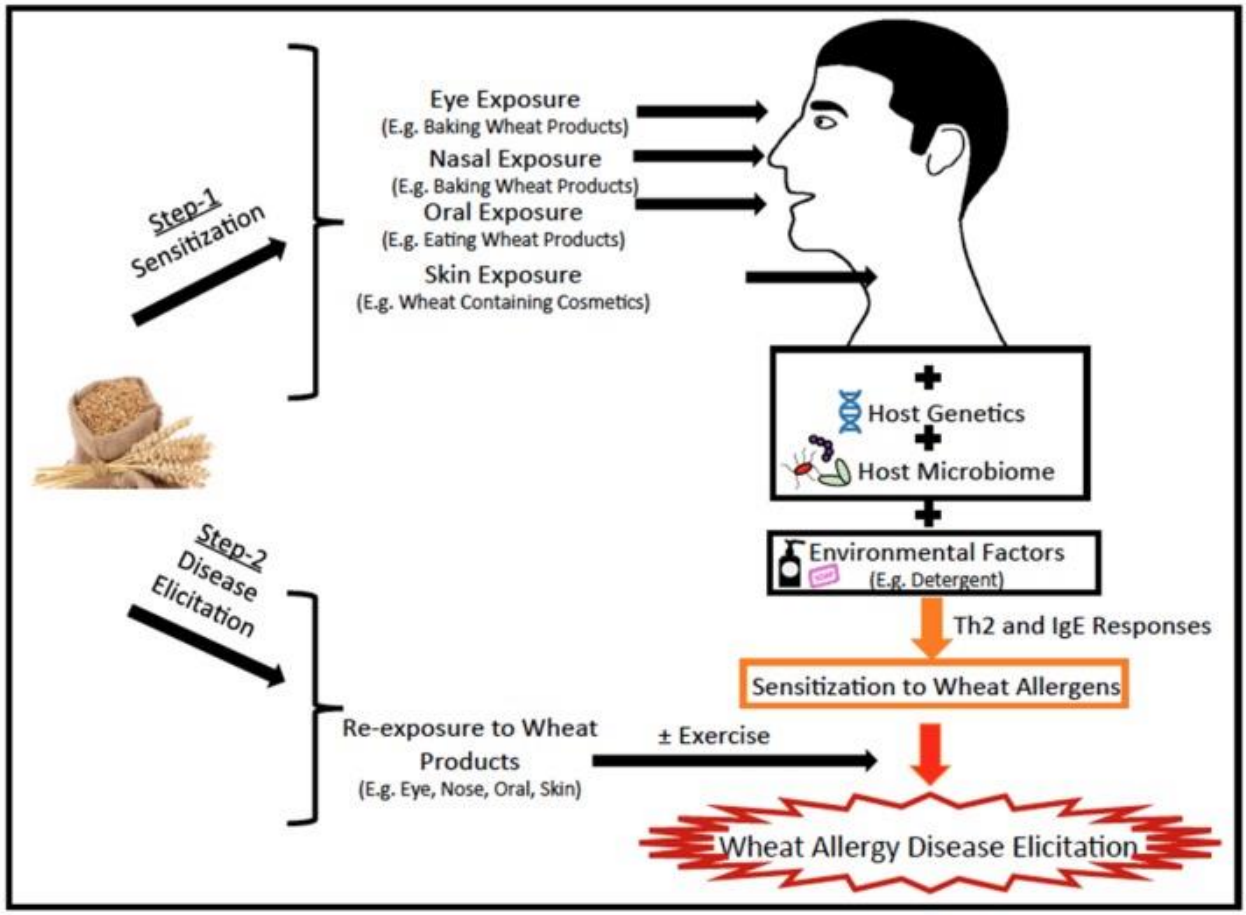

Figure 2. The genesis of wheat allergy: sensitization and elicitation of disease (Quoted from Jin et al.[2]).

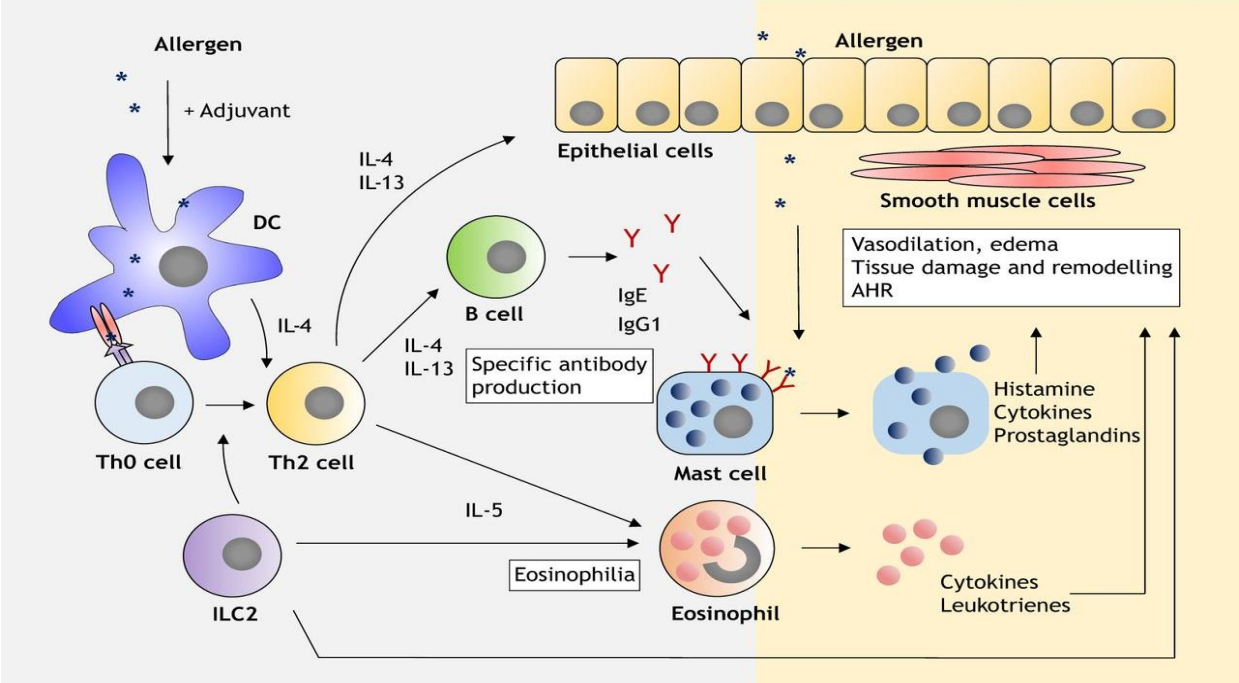

Figure 3. Mechanisms of allergy induction in murine models (Adapted from Spacova et al. [24]).

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