

# Evaluation of Clinical Features of Pediatric Patients with Wheat Sensitivity

## Buğday Duyarlılığı Saptanan Çocuk Hastaların Klinik Özelliklerinin Değerlendirilmesi

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### ABSTRACT

**Objective:** This study aimed to determine the frequency of true wheat allergy among pediatric patients with wheat sensitivity detected by skin prick test (SPT) in our center and to evaluate the clinical features and prognosis of the patients.

**Material and Methods:** This study was conducted with 63 patients who were found to have wheat sensitivity on skin prick test (SPT) between January 2017 and May 2023 in the Pediatric Allergy and Immunology Clinic of our hospital. Demographic and clinical characteristics, oral provocation tests (OPT) and prognosis of these patients were analyzed.

**Results:** In 9432 food SPTs, wheat positivity was detected in 63 patients and the wheat sensitivity rate was found to be 0.6%. Sixty-one point nine percent of these patients were girls. In patients with wheat atopy, 55.5% were infants between 0-6 months of age. Out of 63 patients, six (9.5%) presented with a history suggestive of IgE-mediated reaction, while 57 (90.5%) presented with a history suggestive of atopic dermatitis. Among these patients with a history of atopic dermatitis, 34 (59.6%) were found to have cow's milk and egg atopy in addition to wheat sensitivity. Eczema exacerbation was observed in three patients on OPT performed after 2-4 weeks of short term elimination. These patients were able to consume wheat without any reaction after 6-12 months of elimination diet.

**Conclusion:** Wheat sensitivity not confirmed by oral provocation tests leads to unnecessary elimination of wheat, an essential nutrient. This shows the importance of OPT in patients with wheat atopy.

**Key Words:** Sensitivity, Oral provocation test, Wheat

### ÖZ

**Amaç:** Bu çalışma ile merkezimizde deri prick testi (DPT) ile buğday atopisi saptanan çocuk hastalar içinde gerçek buğday alerjisi sıklığının belirlenmesi, hastaların klinik özelliklerinin ve prognozlarının değerlendirilmesi amaçlanmıştır.

**Gereç ve Yöntemler:** Bu çalışma hastanemiz Çocuk Alerji ve İmmünoloji Kliniği'nde Ocak 2017 ile Mayıs 2023 tarihleri arasında deri prick test (DPT)'lerinde buğday atopisi saptanan 63 hasta ile yapılmıştır. Bu hastaların demografik ve klinik özellikleri, oral provokasyon testleri (OPT) ve prognozları incelenmiştir.

**Bulgular:** Yapılan 9432 besin DPT'nde 63 hastada buğday pozitifliği saptandı ve buğday atopi oranı %0.6 olarak bulundu. Bu hastaların %61.9'u kızdı. Buğday atopisi saptanan hastaların %55.5'i 0-6 ay arasındaki süt çocuklarından oluşmaktaydı. Altmış üç hastadan altı (%9.5)'i IgE aracılıklı reaksiyon düşündürülen öykü ile, 57 (%90.5)'i ise atopik



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**Ethics Committee Approval / Etik Kurul Onayı:** This study was conducted in accordance with the Helsinki Declaration Principles. Ethics Approval was granted by Ankara City Hospital Clinical Trials (according to decision number E2-23-50360).

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dermatit düşündüren öykü ile başvurmıştı. Atopik dermatit öyküsü olan bu hastalardan 34 (%59.6)'sında buğday atopisine ek olarak inek sütü ve yumurta atopisi de saptandı. İki ile dört haftalık kısa eliminasyondan sonra yapılan OPT' de üç hastada egzama alevlenmesi görüldü. Bu hastalar 6-12 aylık eliminasyon diyeti sonrasında buğdayı sorunsuz bir şekilde tüketebildi.

**Sonuç:** Oral provokasyon testleri ile doğrulanmayan buğday atopisi, temel besin maddesi olan buğdayın gereksiz eliminasyonuna neden olmaktadır. Bu durum buğday atopisi olan hastalarda OPT'nin önemini göstermektedir.

**Anahtar Sözcükler:** Duyarlılık, Oral provokasyon testi, Buğday

## INTRODUCTION

Food allergies are an important public health problem that is gradually increasing and adversely affecting the life quality of patients and their parents. Food allergy prevalence is thought to be as high as 10% in developed countries (1,2). Cow's milk, eggs, wheat, soy, peanuts, and fruits are responsible for more than 80% of food-related hypersensitivity reactions (3).

Wheat is the most commonly consumed cereal since it can grow in various climates and is a relatively cheap staple food. Even though the sensitivity rates are higher, the real wheat allergy rate verified by the oral provocation test (OPT) is between 0.2% and 0.5%. Clinical findings of wheat-related hypersensitivity reactions vary depending on the routes of allergen exposure and underlying immunologic mechanisms (4).

Following wheat consumption, it is possible to observe various reactions such as urticaria, angioedema, bronchial obstruction, nausea, stomachache and anaphylaxis characterized by classical IgE-mediated early-type reaction findings. Children commonly develop tolerance to these reactions during their school years, just like milk and egg allergies.

In adolescents, food-dependent exercise-induced anaphylaxis occurs in combination with food intake and physical exercise as well as nonsteroidal anti-inflammatory drugs or alcohol. And also wheat allergy may present with occupational asthma (known as baker's asthma) and rhinitis or contact urticaria-like clinical conditions in these age group (5).

In these study, it was aimed to determine the real wheat allergy rate among pediatric patients diagnosed with wheat sensitivity and to evaluate their clinical characteristics and prognosis.

## MATERIALS and METHODS

The research was carried out at the Pediatric Allergy and Immunology Clinic of Ankara Bilkent City Hospital. Ethics approval was granted by Ankara Bilkent City Hospital Clinical Trials (27.09.2023/E2-23-50360). The study was conducted in accordance with the principles of the Declaration of Helsinki.

SPTs performed between January 2017 and May 2023 were examined retrospectively. Patients who were found to have wheat sensitivity and whose full medical records were accessible were included in the study.

Data such as demographic, presenting complaints of the patients, the duration between wheat consumption and

symptoms, clinical characteristics of the reaction, and accompanying allergic diseases were obtained from the medical records of the patients. Wheat-specific IgE values, existing food atopy, and the SPT results and tolerance statuses were recorded. Wheat-specific IgE below 0.35 kU/L was categorised as negative, between 0.35-100 kU/L as high and >100 kU/L as very high. The patients were categorized according to their ages 0-6 months, 6-12 months, 12-24 months, and >24 months to analyze a detailed evaluation of their diet and developmental characteristics.

**Skin prick test:** This test is applied to flexors on the back or forearm using commercial extracts (Lofarma®, Milan, 1945) and the prick method. As a negative control, 0.9% sodium chloride is used, while histamine hydrochloride serves as the positive control. The results are evaluated 15-20 minutes after application. A pitting of three millimetres or more accompanied by a circle of erythema around the test area is considered a positive result.

In the event of a suspected food-related reaction, the SPT is performed with a food panel including wheat (milk, eggs, wheat, peanuts, fish, and soy). When there is no related clinical history, the positive result of a wheat SPT is accepted as 'sensitivity'. In the case of a compatible clinical history in the SPT positivity, a diagnostic OPT is applied, and the patient is diagnosed with 'wheat allergy' or the allergy is excluded.

**Oral provocation test:** OPT was performed at baseline to confirm the diagnosis of wheat allergy or during follow-up to assess tolerance. OPTs were performed as open OPTs after obtaining written consent from the patient or parent, under the supervision of experienced personnel and taking every precaution for a possible anaphylaxis intervention. All patients were examined in detail before starting OPT. Vital signs and physical examination findings of the patients were recorded. Oral wheat provocation tests were performed according to the Turkish National Allergy and Clinical Immunology Society Food Loading Tests: According to the 2019 Guidelines of the National Allergy and Clinical Immunology Society of Türkiye and it was performed using pasta equivalent to 10 grams of wheat protein without any other product in wheat. The oral provocation test was started with 0.01 grams of wheat protein and terminated when the equivalent of 10 grams of wheat protein was reached (6). Patients were kept under observation for at least two hours after the last dose was given, and in case of a reaction, until the symptoms completely regressed. If objective findings were present during OPT, the test was considered positive, the test was terminated and the reaction was treated as required. If

negative, food was added to the diet. At this stage, clinical follow-up of the patient was continued in terms of late reactions.

**Statistical analyses:** Statistical analysis was performed using SPSS version 22.0 (SPSS Inc. Chicago, IL, USA). Numbers and percentages were reported for discrete variables. Continuous variables were expressed as mean, minimum and maximum for data with a normal distribution and as median and interquartile range (IQR, 25<sup>th</sup>–75<sup>th</sup> percentile values) for non-normally distributed data. A value of  $p < 0.050$  was considered statistically significant.

## RESULTS

Wheat sensitivity was detected in 63 of 9432 patients who underwent food SPT, including wheat, during the study period and the wheat sensitivity rate was 0.66%. Of the patients, 61.9% were girls. The average age at admission was 16 months. The median age was 6 months (4 months to 8.5 months, IQR; 5 months). When considering the most common age group for initial presentation, 55.5% were infants aged between 0 and 6 months. Only six patients (9.5%,  $n = 63$ ) were over 24 months old at the time of initial assessment.

When the patients are evaluated according to their complaints, six patients (9.6%,  $n = 63$ ) at the age of 5-132 months had a skin rash after wheat consumption, suggesting an IgE-mediated reaction, and 57 (90.4%,  $n = 63$ ) patients presented due to skin lesions, which suggested atopic dermatitis (AD). The age and gender characteristics of patients with wheat sensitivity are summarized in Table I.

One of the patients (a 5-month-old boy) with the complaint of a skin rash had a high wheat-specific IgE value of 62.8 kU/L, while the other five patients had a low wheat-specific IgE value (under 0.35 kU/L) at admission. All patients underwent a

**Table I: Demographic and clinical characteristics of patients with wheat sensitivity (n= 63)**

Parameter	
Age at wheat atopy, months (median-IQR)	16 (6.5)
Sex*	
Male	24 (38.1)
Female	39 (61.9)
Age groups*	
0-6 months	35 (55.5)
6-12 months	19 (30.1)
12-24 months	3 (4.8)
>24 months	6 (9.6)
Application complaint*	
IgE-mediated reaction	6 (9.6)
Male	3 (4.8)
Female	3 (4.8)
AD	57 (90.4)
Male	21 (33.3)
Female	36 (57.1)

\*  $n(\%)$

**Table II: Laboratory findings according to age groups.**

Age group / n (%)	Total IgE* (IU/mL)	Eosinophil Number* ( $\times 10^7/L$ )	Eosinophil Percentage (%)
0-6 months / 35 (55.5)	155.6	903	7.5
6-12 months / 19 (30.1)	614	703.3	5.2
12-24 months/ 3 (4.8)	209.9	343	3.3
>24 months/ 6 (9.6)	492.8	350	3.1
Total (n= 63)	315.2	769.4	6.4

\*mean

**Table III: Wheat specific IgE status according to clinical features (n= 63)**

Parameter	n (%)
Wheat specific IgE	63 (100)
Low	34(54)
High	29 (46)
Very High	0 (0)
IgE-mediated reaction	6 (9.6)
Low	3 (4.8)
High	3 (4.8)
Very High	0 (0)
AD	57 (90.4)
Low	31(49.2)
High	26 (41.2)
Very High	0 (0)

diagnostic OPT at admission, and none of them showed acute reactions. Therefore, wheat was added into their diet without any issues and so wheat allergy was excluded. Additional food sensitivity was not detected by SPT in any of these patients.

Most of the patients ( $n = 34/57$ , 59.60%) who had skin lesions, which suggested AD, consisted of 0-6 months old infants. Fifty-two of these patients (91.2%) had additional food sensitivity. Fifteen of the patients (26.3%) had accompanying egg atopy, three (5.20%) had milk atopy, and 34 (59.60%) had both milk and egg atopy. The patients' atopy pattern is summarized in Figure 1.

The mean total IgE level of the patients was 315.20 IU/mL (1.5-525) and eosinophil number was  $769.4 \times 10^7/L$  (60-1100) at admission. The data are summarized in Table II.

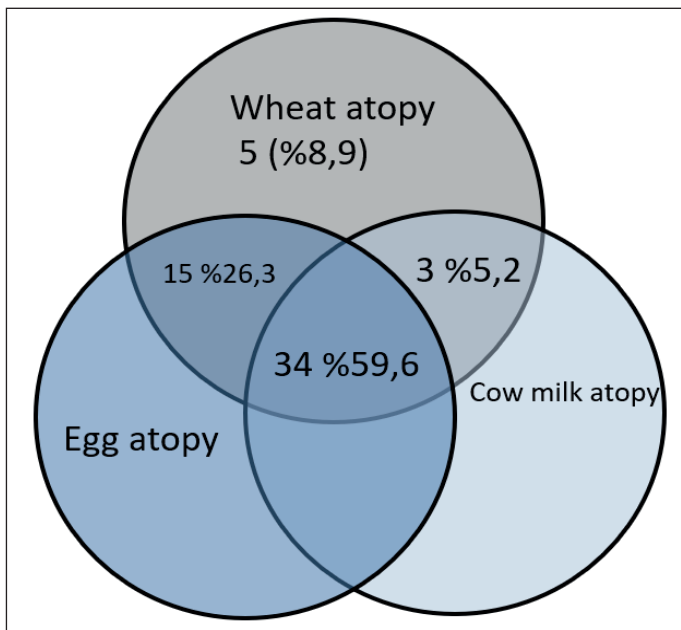
Table III summarizes the distribution of wheat sp IgE levels in 57 patients admitted with atopic dermatitis. Of these patients, 29 (50.9%) had low levels below 0.35 kU/L, while 28 (49.1%) had high levels between 0.35-100 kU/L. No patient had a wheat sp IgE value above 100 kU/L.

It was observed that the patient, who presented with atopic dermatitis clinic, and/or his mother when he was breastfeeding, was recommended short-term wheat elimination for 2-3 weeks, and then wheat was added to his diet in the form of a food appropriate for his age. While 54 (94.7%,  $n = 57$ ) patients consumed wheat without any eczema exacerbations, in the

**Table IV: Characteristics of patients with wheat allergy confirmed by Oral Food Challenge (OFC)**

Admission	Wheat SPT at admission (mm)	Wheat-specific IgE at admission (kU/L)	Elimination diet duration (months)	Before OFC Wheat sp IgE (kU/L) at the end of elimination
3 m/M	3 mm	23.90	12	0.43
4 m/F	5 mm	1.90	9	<0.35
6 m/M	4 mm	19.80	6	<0.35

**m:** Months, **F:** Female, **M:** Male



**Figure 1:** Association of cow's milk and egg atopy in atopic dermatitis patients with wheat atopy.

other three (5.3%, n= 57) , who had multi-food atopy and wheat specific IgE increase, eczema exacerbation was observed. The clinical characteristics of these patients are summarized in Table IV.

## DISCUSSION

There are many studies in the literature evaluating the characteristics of food allergies, especially milk and egg allergies, in childhood; however, the data on wheat allergy are rather limited. The aim of our study was to evaluate the clinical and prognostic characteristics of patients diagnosed with wheat atopy and wheat allergy.

Wheat is regarded as a staple food around the world. In our country, wheat is included in diets starting from a very young age in various forms, primarily as bread. However, wheat allergy is not a widely known phenomenon. Although the real wheat allergy prevalence verified by OPT is not known clearly, it is estimated to be less than 0.5% in the general population (7). The data obtained from positive SPTs indicate that up to 3% of the general American pediatric population is sensitive to wheat; however, the allergy rate is estimated to be between 0.2% and 1% (7). In another study, in which 256 children patients were

evaluated, while the sensitivity to wheat was 9.4% by SPT, the real wheat allergy verified by OPT was 0.4% (8). It was stated that wheat allergy is the third most common food allergy after milk and egg in countries such as Germany, Japan, and Finland and that its prevalence varies according to age and geographic region and is thought to be 1% (0.4%-4%) (9). In the studies of Unsal et al. (10) where they evaluated 613 pediatric patients with food atopy, wheat sensitivity was detected in 37 (6%) patients, and in wheat OFCs, real wheat allergy was diagnosed in 2.6% of children under 2 years of age and in 2.8% of those between 2-18 years of age. In our study, both the wheat atopy rate (0.6%) and the confirmed wheat allergy rate (0.03%) were found to be much lower than literature data.

Wheat is usually introduced into the diet of infants between 4 and 6 months of life, but sensitivity can develop much earlier through breast milk or extra-intestinal exposures such as skin and rhinoconjunctival (11). The fact that sensitivity was detected in the infantile period between 0-6 months in the majority of patients (55.5%) in our study supports this data.

When the complaints of our patients were evaluated, no acute reactions were observed in those who underwent a diagnostic OPT following their referral to the center due to a skin rash occurring shortly after wheat consumption, suggesting an early IgE-mediated reaction. Wheat was added into the diet of these patients and wheat allergy was excluded. In our study, no patients describing severe IgE-mediated reactions to wheat. Considering the literature, in a study in which the clinical characteristics of 100 children experiencing IgE-mediated reactions due to wheat consumption were evaluated, the researchers stated that while only the skin and mucosa were affected in 49 patients, 51 patients had anaphylaxis. SPT size and wheat-specific IgE were found to be a significant predictor for anaphylaxis. Although there are studies that show how wheat-specific IgE predicts reaction severity, it must be noted that there might be cases of anaphylaxis development despite low specific IgE values (12,13).

In another study where OPT results were evaluated in 108 children with an average age of 1.5 years due to suspicion of wheat allergy, the test was found to be negative in approximately half of the patients and wheat could be added to the diet (4). While this procedure is difficult to apply to pediatric patients, that study showed the significance of OPT application during the diagnostic process in an environment equipped with opportunities for a possible anaphylaxis intervention.

In previous studies, the most common application symptom associated with wheat consumption was moderate severity AD (5). A similar picture was also seen in our study, with a large portion of our patients (90.4%) presenting to our center with the same history. In such food allergies, observing recovery in lesions by short-term elimination and, later on, added the food into the diet are diagnostic in cases of re-exacerbation. Following this diagnostic provocation applied in our patients, wheat was associated with exacerbation of eczematous rash in only three (5.20%). Wheat was added into the diet of the other children without any reactions.

AD is known to be the most powerful and best-known risk factor for developing food allergies. This is explained by the dual allergen exposure hypothesis, which suggests that allergic sensitivity to food might originate from cutaneous exposure, and the disturbed skin barrier in atopic dermatitis results in increased permeability for food allergies (14,15). Examination of the literature reveals that wheat atopy is the third most common atopy after milk and eggs in patients with AD (8,16). In our study, 15 (26.3%) patients had egg atopy, 3 (5.2%) patients had milk atopy, 34 (59.6%) patients had both wheat and egg atopy, and three patients with OFC and eczema exacerbation had both milk and egg atopy, indicating that wheat atopy should be considered in cases of AD not responding to milk and egg diet.

There is very limited literature data on the prognosis and natural course of wheat allergy. Keet et al. (17), who evaluated 103 patients with wheat-related IgE-mediated clinical history diagnosed with SPT-positive results and showed tolerance by OPT, found the mean tolerance age to be 79 months. They highlighted that wheat specific IgE is the most significant prognosis indicator, and tolerance might be delayed up to adolescent age in those with values over >50 kU/L; however, those with delayed tolerance were a minority. Additionally, there some patients developed tolerance earlier despite having high specific IgE values. However, it is difficult to determine when children have their peak specific IgE values. Compared to other food allergies, specific IgE is less helpful in predicting clinical reactivity. At this stage, since the related molecular mechanisms are not entirely understood, there are no treatments for wheat allergy except for oral immunotherapy, and avoiding food with wheat is the best option. The patients should be periodically tested by OPT, and their tolerance status must be evaluated (17, 18).

In conclusion, skin test positivity that cannot be verified by OPT can cause unreal food allergy stigma, the patients to unnecessarily eliminate foods, and nutritional deficiency that might result from removing a staple food from their diet, such as wheat. This indicates the significance of diagnostic OPTs. Additionally, SPT size and specific IgE cut-off values, which can predict severe reactions to wheat, are not as clear-cut as for milk and eggs. This requires the provocation tests to be performed by experienced healthcare staff in an environment equipped with emergency intervention facilities.

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