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# Wheat sensitization in allergic children from Mumbai, India - A retrospective study

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## Abstract

***Background and Objectives*****:** Wheat is a major constituent of many foods in Asia. It is known to cause allergies involving the respiratory system, skin, and gut. There is to date no data on wheat sensitization in children presenting with allergies in Mumbai, India. The present study evaluated the magnitude and significance of wheat sensitization in allergic Indian children attending our clinic. ***Study design and settings:*** The study is a retrospective analysis of children with allergy attending our clinic in Mumbai, India. ***Subjects and Methods*****:** The records of children < 18 years of age with allergies were evaluated demographically, anthropometrically, clinically, and blood allergy testing compared and analysed for clinical significance, if any. ***Results*****:** Out of the 175 children with allergic manifestations, 53 (30.3%) had positive serum wheat-specific IgE levels (wheat-specific IgE > 0.35 kUA/L). Children with wheat-specific IgE positivity had significantly higher total serum IgE levels compared to wheat IgE-negative allergic children (1071.9 vs 405.7 IU/ml, p=0.000236). The former group also had multiple sensitizations to other food and aero-allergens. But the number and type of body system involved, family history of allergies, and weight of the children in the two groups were not statistically different. ***Conclusion:*** Wheat sensitization is observed in one-third of allergic children in Mumbai. These children have sensitization to other food and inhaled allergens but no particular system predilection occurs in them.

**Keywords:** Wheat hypersensitivity, IgE, Atopic dermatitis, Asthma, Allergic rhinitis.

## INTRODUCTION

Wheat is incorporated in many foods in Asia. Wheat allergy is an allergic reaction of varying severity to wheat-containing foods. It may present as skin rashes or urticaria, nasal congestion, throat irritation, cough, breathing difficulty, or gastro-intestinal symptoms [1]. Often true wheat allergy that is IgE-mediated is confused with celiac disease. Celiac disease is gluten intolerance and an autoimmune-mediated disease. The consumption of gluten-containing foods in such patients leads to small intestinal villi damage (Figure 1) [2].

Wheat-allergic children usually manifest with food allergy symptoms or wheat-dependent, exercise-induced anaphylaxis. Diagnosis rests on medical history and determination of wheat-specific IgE or skin prick tests. However, the diagnostic gold standard is oral wheat challenge that clinches the diagnosis [3]. Wheat allergy prevalence varies as per the region, age group studied, and the testing method used [4]. True wheat challenge-proven allergy is lesser than wheat sensitization but the cut-off limit of values of wheat IgE for diagnosis is less clear [5]. Wheat allergy prevalence was 0.21% in the people in Japan [6]. On the other hand, in Europe the prevalence of food challenge-proven wheat allergy was found to be 0.1-0.6% [7]. Children, bakers and flour mill workers are noted to have higher incidence [3]. Positive serum IgE antibodies to wheat were present in 0.4 to 3.6% of children < 14 years of age [8].

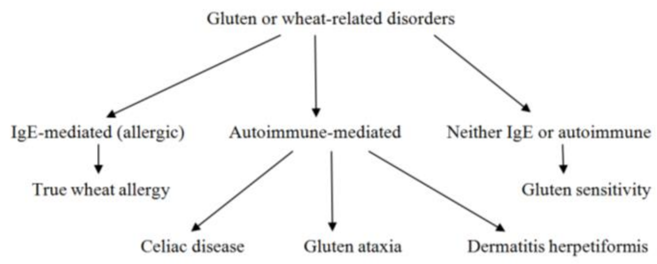


**Figure 1:** Pathogenesis-based classification of gluten-related disorders

Around 65% of children with wheat allergy outgrow it by the age of 12 [1, 9]. But children with food allergies in early life are more likely to develop asthma and allergic rhinitis than the non-allergic children [10, 11].

There has to date been no studies of the prevalence of wheat sensitization in Indian allergic children. Hence, we undertook this evaluation to determine wheat sensitization in children presenting with suspected allergy in our clinic. We compared their demographical parameters, clinical presentation, presence of other food and aero-allergenicity, and its impact on weight and serum total IgE levels.

## SUBJECTS AND METHODS

The retrospective data of children ≤ 18 years of age presenting with suspected allergic symptoms at our clinic in Mumbai, India and with comprehensive blood allergen testing reports were analyzed. The Internal Review Board had approved the study. The detailed history, age and gender of the children were noted and findings of a thorough clinical examination jotted down. Family history of allergies was looked into. The height and weight were recorded.

The results of total serum IgE levels and serum specific IgE to wheat and 28 other allergens was noted. Appropriate selection of allergens was done in each case based on their clinical history. The allergens tested included food allergens such as milk, soya, cheese, egg white, chicken meat, shrimp, corn, apple, carrot, banana, etc. and aeroallergens such as cat epithelium, dust mite, cockroach, grass pollen, fungus, etc. ImmunoCAP technology of Pharmacia Diagnostics AB, Sweden was employed for this testing. The test has enhanced sensitivity, specificity, reliability, and reproducibility compared to other *in vitro* allergy tests [12]. The children were grouped into two categories: those with positive serum wheat specific IgE and those whose blood did not demonstrate positivity to the wheat allergen. Positivity was considered when the specific IgE levels were ≥ 0.35 kUA/L (Kilo units of allergen/liter) [13]. The results were graded based on the specific IgE levels into Grade I= 0.3-0.69, Grade II=0.7 to 3.49, and Grade III=3.5-17.49 kUA/L. None of the children had wheat-specific IgE levels >17.49 kUA/L. The demography, clinical manifestations, family history of allergies, weight, total IgE levels, and positivity of other aeroallergens and food allergens were compared in these two groups and tested for statistical significance.

### Statistical Analysis

Statistical analysis was carried out by student's t test for numerical data and chi-test for categorical data. Statistical significance was considered when the p value was < 0.05 [14].

## RESULTS

175 children formed our study group. There were 82 females and 93 males with a male: female ratio of 1:1.13. The mean age was 4.5688+/-3.02816 with a range of 5 months to 15 years. Out of these 175 allergic children, 53 (30.3%) children tested positive to wheat allergen and 122 had negative wheat-specific IgE results. These two groups of children were matched for age and gender (Table 1). Family history of allergy was elicited in 61 children in wheat non-sensitized group and 27 children in the wheat sensitized group. The difference was not statistically significant (50 vs 50.9%, p=0.9). The weight was normal in 84 (68.85%) children in the wheat-negative group and 35 (66.04%) children in wheat-positive group. Twelve (9.84%) and 7 (13.21%) children in wheat-negative and wheat-positive groups respectively had weights lesser than normal for age. The weight was on the obese side in 26 (21.31%) in wheat-negative group and 11 (20.75%) in wheat-positive group. But these differences were not found to be of statistical significance (ANOVA, p value=0.179416) (Table 1).

In the wheat-negative group, allergic conjunctivitis was present in 51 (41.8%) children while it was seen in 25 (47.17%) children in the wheat-sensitized group. Atopic dermatitis was the symptom in 90 (73.77%) children in wheat-negative group and 42 (79.25%) in the other group. Nose allergy was noticed in 87 (71.31%) children in wheat-negative group and 39 (73.58%) in the second group. Additionally, chronic cough and wheezing was the clinical presentation in 100 (81.97%) patients in the wheat-negative group and 42 (79.25%) in the wheat-sensitized group. All of these differences in clinical manifestations were found to be statistically insignificant (Table 1). One child in the wheat-negative group had loose motions as the clinical features and no other allergic symptoms.

The systems involved in these allergic children were eyes, skin, nose, and lungs. 18, 25, 42, and 36 children in the wheat-negative group had one, two, three, and all systems involved with allergy respectively. While in the wheat-sensitized group, 7, 11, 19, and 16 children were similarly affected. But the difference in these two groups as regards number of systems involved with allergy was insignificant (ANOVA, p value= p=0.163044) (Table 1).

**Table 1:** Demographic and clinical details of the studied children

| Parameter | Wheat IgE negative (n=122) | Wheat IgE positive (n=53) | p value |
|---|---|---|---|
| Mean age ± SD (years) | 4.72 ± 3.12 | 4.23 ± 2.79 | 0.325 |
| Females | 54 | 28 | 0.29 |
| Family history of allergy present [n(%)] | 61(50) | 27 (50.94) | 0.9 |
| Weight for age Normal, low, and high [n(%)] | 84 (68.85), 12 (9.84), 26(21.31) | 35 (66.04), 7 (13.21), 11 (20.75) | ANOVA, p=0.18 |
| Allergic conjunctivitis [n(%)] | 51(41.8) | 25(47.2) | 0.51 |
| Atopic dermatitis [n(%)] | 90(73.8) | 42(79.25) | 0.44 |
| Allergic rhinitis [n(%)] | 87(71.3) | 39(73.6) | 0.76 |
| Wheezing/Asthma/CVA [n(%)] | 100(81.97) | 42(79.25) | 0.67 |
| Number of systems involved [1, 2, 3, 4][n(%)] | 18 (14.75), 25 (20.49), 42 (34.42), 36 (29.5) | 7 (13.2), 11 (20.75), 19 (35.85), 16 (30.19) | 0.16 |

CVA=Cough variant asthma

Total IgE estimation was available in 120 children in the wheat-negative group and in 52 in the wheat-sensitized group. The mean value was 405.7 and 1071.88 IU/ml in the two groups respectively. This difference was statistically highly significant with p value of 0.000236. The values were high for age in 37 children in the first group and 30 in the second group. This difference was also highly significant (30.83% vs 57.7% respectively, p value=0.00000794).

Based on the values of specific IgE, there are seven grades from 0 to 6. In our study, 21 children in the wheat-positive group were in grade 1, 28 in grade 2, and only 4 were in grades 3-6 with specific IgE values of 3.5 and above kUA/l (mean=1.521961+/-2.537963, range=0.37 to 13.8 kUA/l) (Table 2). Some of these children also had other multiple allergen positivity on specific IgE testing. In the group with negative specific IgE to wheat allergen, 23 also had negative serum tests for all the other 28 allergens tested. 11 in this wheat IgE negative group had positive report to just one allergen which was not wheat, 13 had to 2, 7 had to 3, and 68 had to >3 allergens. But in the wheat-positive group, children had positive results to at least two or more allergens. This implied that all the children had specific positivity to at least one allergen besides wheat. One child each had 2 and 3 specific allergen positivity and the remaining 51 children demonstrated more than 3 specific allergen positivity. The difference in proportion of children in these two groups who had more than 3 allergen positivity revealed high statistical significance (55.74 vs 96.23%, p=0. 000000132). The mean number of allergens in the two groups that came up as positive were 5.53+/-5.65 vs 15.74+/-8.18, $p=1.47x10^{-7}$ (Table 2).

**Table 2:** Total IgE and specific IgE in wheat-non-sensitized and wheat-sensitized group

| Investigative parameter | Wheat-non-sensitized group | Wheat-sensitized group | p value |
|---|---|---|---|
| Total IgE frequency (n) | 120 | 52 | |
| Total IgE value ± SD (IU/ml) | 405.7 ± 781.83 | 1071.88 ± 1522.305 | 0.000236 |
| High total IgE for age (n) | 37 (30.83) | 30 (57.7) | 0.00000794 |
| Mean wheat specific IgE ± SD (kUA/l) | 0.09 ± 0.07 | 1.522 ± 2.54 | <0.05 |
| Wheat IgE grades [0, 1, 2,≥3] | [122, 0, 0, 0] | [0, 21, 28, 4] | --- |
| No. of allergens positivity [0, 1, 2, 3, >3] | [23, 11, 13, 7, 68] | [0, 0, 1, 1, 51] | --- |
| Children with 3 or more allergen positivity [n(%)] | 68 (55.74) | 51 (96.23) | <0.05 |
| Mean allergen index | 5.53 ± 5.65 | 15.74 ± 8.18 | <0.05 |
| No. of food allergen positivity [0, 1, 2, 3, >3] | [36, 15, 27, 12, 32] | [0, 0, 1, 6, 46] | --- |
| Children with 3 or more food allergen positivity [n(%)] | 32 (26.23) | 46 (86.79) | <0.05 |
| Mean food allergen index | 2.48 ± 2.74 | 8.62 ± 4.54 | <0.05 |
| No. of aeroallergen positivity [0, 1, 2, 3, >3] | [46, 14, 5, 11, 46] | [3, 6, 3, 4, 37] | --- |
| Children with 3 or more aeroallergen positivity [n(%)] | 46 (37.7) | 37 (69.8) | <0.05 |
| Mean aeroallergen score | 3.06 ± 3.56 | 7.11 ± 4.64 | <0.05 |

When children with wheat IgE-negativity were evaluated for other food allergens, 36 tested negative for other food allergens as well. 15 of the 122 in this group had specific IgE positive to one food item other than wheat, 27 to 2 food allergens, 12 to 3 food allergens and 32 to more than 3 food allergens. But in the wheat IgE positive group, 1 child had positivity report to one food allergen besides wheat, 6 had positivity to 3 food allergens including wheat, and 46 had allergy to more than 3 food allergens tested. When children in the wheat IgE-negative and positive groups were compared, 32/122 (26.23%) and 46/53 (86.79%) had positive specific IgE to more than 3 food allergens ($p=1.3x10^{-13}$). The mean food allergen score was 2.48+/-2.74 and 8.62+/-4.54 respectively with $p=8.5x10^{-22}$.

Aeroallergens tested were separately evaluated in the two groups. It was seen that 46 patients with wheat IgE negative result had no aeroallergen positive report. 14 in this wheat-negative group tested positive for 1aeroallergen, 5 to 2 aeroallergens, 11 to 3 aeroallergens, and 46 to >3 aeroallergens. On the other hand, 3 children in the wheat IgE positive group had sensitization to no aeroallergen tested. But in the same group, 6 had one aeroallergen positivity, 3 had 2, 4 had 3, and 37 had >3 aeroallergen positivity. Thus children with high specific IgE to more than 3 aeroallergens was 46/122 (37.7%) in wheat-negative group and 37/53 (69.8%) in wheat-positive group (p=0.000093). The mean aeroallergen index in these two groups was 3.06+/-3.56 and 7.11+/-4.64 respectively, p value=$2.42x10^{-9}$.

The wheat-sensitized group also had higher percentage of co-existent milk, cheese, soya, almond, coconut, egg white, and chicken meat allergy. Amongst the sea foods, tuna and salmon allergy was significantly more common in the wheat-sensitized group. But cod and shrimp allergy was equally prevalent in both the groups (Table 3). Peanut, corn, apple, carrot, cabbage, banana, and mango allergy were prominent in the wheat-positive group but not casein or cocoa allergy. Potato allergen was carried out only in 18 patients and it was significantly more in the wheat-positive group (p=0.015). Both groups had almost similar percentage of baker's yeast IgE positivity (7.4 vs 7.14% in wheat-negative and wheat-positive groups respectively, p=0.97). Orange and rice allergen testing did not yield significant high in wheat-positive group (p=0.14 and 0.08 respectively). Only one child had high orange IgE level and he was also allergic to all the pollens (grass, weed, and tree) and to wheat and apple [15]. Strawberry allergen test was done in only10 patients (6, 4) and it was positive in 2 children out of 4 in wheat-positive group. Green pea, grape, tomato, and cauliflower was tested in only 4(3, 1), 9 (8, 1), 3 (1, 2) and 3 (3, 0) patients respectively and the sample size was too small for inference. Spinach, pear, cashew, malt, and melon allergy were tested in 1, 2, 1, 1 and 1 children respectively only in wheat-negative group and these were not elevated. Mushroom was tested in 16 patients and it was positive in none of them. 2 (1, 1) children had allergen testing for lemon and it was negative in both. Onion was tested in only one child and it was normal.

**Table 3:** Specific IgE to various foods other than wheat

| Food allergen tested | Wheat-IgE-negative (High/Normal) | Wheat-IgE-positive (High/Normal) | p value |
|---|---|---|---|
| Milk | 21/101 | 37/15 | <0.05 |
| Cheese | 2/93 | 15/22 | <0.05 |
| Soya | 0/121 | 17/35 | <0.05 |
| Almond | 0/90 | 6/24 | <0.05 |
| Coconut | 6/111 | 24/25 | <0.05 |
| Egg white | 26/96 | 38/15 | <0.05 |
| Chicken meat | 3/117 | 6/45 | <0.05 |
| Tuna | 7/114 | 13/39 | <0.05 |
| Salmon | 2/61 | 5/17 | <0.05 |
| Cod | 1/55 | 2/16 | 0.081 |
| Shrimp | 23/97 | 15/34 | 0.105 |
| Peanut | 1/26 | 4/4 | <0.05 |
| Corn | 1/62 | 12/19 | <0.05 |
| Apple | 1/61 | 9/20 | <0.05 |
| Carrot | 0/67 | 8/25 | <0.05 |
| Cabbage | 0/54 | 6/17 | <0.05 |
| Banana | 3/39 | 10/8 | <0.05 |
| Mango | 0/16 | 4/5 | <0.05 |
| Casein | 2/23 | 4/12 | 0.13 |
| Cocoa | 0/22 | 2/11 | 0.058 |
| Potato | 0/13 | 2/3 | <0.05 |
| Baker's yeast | 2/25 | 1/13 | 0.97 |
| Orange | 0/14 | 1/6 | 0.15 |
| Rice | 0/8 | ½ | 0.08 |
| Strawberry | 0/6 | 2/2 | 0.052 |

Both types of house dust mite, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* and house dust greer tested positive in significantly more children in wheat-sensitized group (Table 4). But cockroach IgE was not significantly higher in wheat-positive children (27.05 vs 37.25% in wheat-negative and positive groups respectively, p=0.18). More children in the wheat-sensitized group had associated cat epithelium, dog epithelium, and pigeon droppings sensitization.

Allergy to parrot feathers was tested in 33 children (27 in wheat-negative and 6 in wheat positive children) but no positive reports emerged. The fungi (*Cladosporium herbarum, aspergillus fumigatus*, and *candida albicans*) allergens, grass pollens, weed pollens, and tree pollens IgE were higher in significantly more children in the wheat positive group (Table 4). Rabbit epithelium IgE was estimated in only 3 patients and was normal in all 3.

**Table 4:** Specific IgE to aeroallergens

| Aeroallergen tested | Wheat-non-sensitized group (High/Normal) | Wheat-sensitized group (High/Normal) | p value |
|---|---|---|---|
| *Dermatophagoides pteronyssinus* | 55/67 | 32/19 | 0.03 |
| *Dermatophagoides farinae* | 52/70 | 33/17 | 0.005 |
| House dust greer | 43/77 | 29/21 | 0.007 |
| Cockroach | 32/90 | 20/31 | 0.089 |
| Cat epithelium | 3/43 | 3/14 | <0.05 |
| Dog epithelium | 4/37 | 5/10 | <0.05 |
| Pigeon droppings | 10/67 | 11/23 | <0.05 |
| Parrot feathers | 0/27 | 0/6 | --- |
| *Cladosporium herbarum* | 0/53 | 2/16 | <0.05 |
| *Aspergillus fumigatus* | 0/122 | 12/38 | <0.05 |
| *Candida albicans* | 8/113 | 15/35 | <0.05 |
| Sweet vernal | 1/120 | 16/34 | <0.05 |
| Rye | 3/99 | 31/15 | <0.05 |
| Velvet | 2/116 | 19/31 | <0.05 |
| Mugwort | 6/109 | 14/36 | <0.05 |
| Bermuda Grass | 8/114 | 21/29 | <0.05 |
| Timothy Grass | 5/115 | 16/34 | <0.05 |
| Alder | 0/46 | 2/13 | <0.05 |
| Birch | 1/45 | 3/12 | <0.05 |

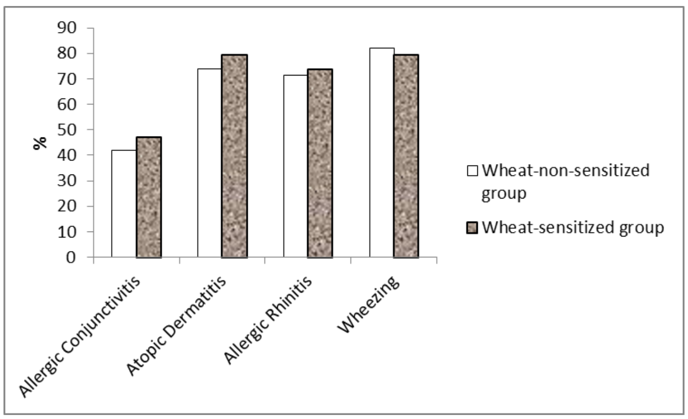


**Figure 2:** Distribution of allergic phenotypes in the two groups

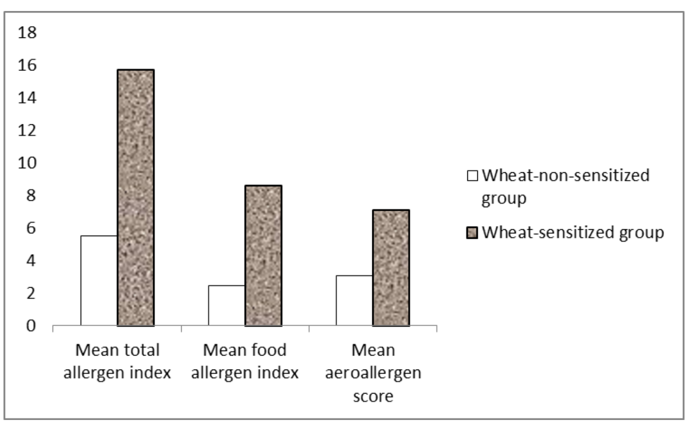


**Figure 3:** Mean allergen score in the two groups

## DISCUSSION

Wheat is an important constituent of food items consumed worldwide. But in some people, it could be allergenic and cause skin, respiratory, and gut allergies. Young children are especially susceptible to it. The prevalence of sensitization to wheat in Indian allergic children has not been estimated to date. We carried out this study in order to determine the percentage and characteristics of allergic children who have elevated wheat allergen IgE levels. Our study is the first of its kind done on allergic children in Mumbai. It could form a baseline for temporal assessment of wheat sensitization in children. It showed that 30.3% of children with allergies have wheat sensitization. They present variably and have poly-allergies but there is no specific body organ predominantly affected.

ImmunoCAP technology for specific allergen IgE level determination is a good *in vitro* test and we used it in these children to detect wheat sensitization in them. Though oral food challenge is considered the gold standard for diagnosis of clinical food allergy, the test is labor-intensive and potentially risky. ImmunoCAP-determined specific-IgE test is a reliable diagnostic tool with a sensitivity of 84-95% and a specificity of 85-94% [16]. Moreover, it gives good determination of nut, wheat, and such food allergies [17]. We were unable to confirm our results with food challenges in these children. Hence children in our study with high wheat IgE are wheat-sensitized and not necessarily wheat-allergic. Studies have shown that food-challenged verified allergy is usually lower than that reported by *in vitro* results [18]. Therefore, our study might report a higher proportion of wheat sensitized children than the actual figures of wheat allergy. Besides, the cut-off for specific IgE levels at which 50% pass rate of food challenges could be expected varies for the different allergens. For wheat, the exact value has not been clearly determined [5]. In our study, by convention, we took the value 0.35 kUA/L as a common cut-off to determine sensitization to a particular allergen. But Graham F *et al* did a retrospective review of the children at their allergy unit and found that the optimal cutoff point for wheat IgE was 12 kUA/L and it gave a specificity of 70% and a sensitivity of 66.67% [19]. Though some studies demonstrated a good correlation of ω-5 gliadin-IgE with oral wheat challenge outcome and clinical wheat allergy, other studies did not find such correlation [20, 21].

All the 175 allergic children were also tested for 28 other food allergens and aeroallergens but the items tested varied. With some of the allergens such as onion, malt, strawberry, lemon, cashew, the number of children with these results were very few and hence they could not be compared for significance in the two groups.

The one child in our study who had orange sensitization also had pollens, wheat, and apple sensitization [15]. Most of orange allergy is in the form of oral allergy syndrome with throat irritation and itching. Our child with orange sensitization had allergic dermatitis and bronchial asthma. Studies have shown that children with wheat allergy have a favorable prognosis and most of them outgrow it by their teens [9]. But we do not have any longitudinal data on these patients.

In our study, we found that the children in the age group of 0-18 years had 30.3% wheat allergen sensitization. Thai scientists found that 22.2% of allergic children < 1 year of age had wheat sensitization by SPT [22]. Another study from Calcutta revealed that in children <16 years of age with respiratory allergy, a significant number of them had sensitization to brinjal, prawn, banana, spinach, and egg [23]. Our study included children with all types of suspected allergies and was not limited to respiratory allergy.

In our study, none of the 175 children tested had anaphylactic symptoms. They had suspected skin, nose, eye, and respiratory tract allergy symptoms. 132 children had atopic dermatitis and wheat allergen IgE positivity was noted in 42 (31.81%) of them. Food sensitization was observed in 81.06% of our children with atopic dermatitis. Similar findings were observed by Caffarelli C *et al* who found food allergy in 40-90% of children with atopic dermatitis [24]. In the Danish Calmette Study in Kolding, the researchers followed up 1241 children who received BCG at birth for allergy, atopic dermatitis, and allergic sensitization at 13 months of age. 8.4% of the children had sensitization mainly to food items. Atopic dermatitis was observed in 19% of children and these had sensitization to egg, peanut, wheat, cat, and dog [25]. 79.25% of our children with elevated wheat-IgE had atopic dermatitis. We also found that 93.44% of our children with atopic dermatitis had allergic sensitization whereas only 76.7% of children with no atopic dermatitis had allergic sensitization (p= 0.0013).

In our series, 16 out of 21 patients [76.19%] with timothy grass-IgE positive were also sensitized to wheat. Nilsson N *et al* found that 60% of their grass-pollen-positive children were sensitized to wheat (median wheat-IgE was 0.5 kUA/L). In their study, grass-allergic children had low levels of true wheat sensitization as well as cross-reactivity to wheat [26]. These also had history of past or present allergy to other food items such as egg, soy, and fish. Similarly, German researchers Matricardi PM *et al* did a follow-up study on 273 children from birth to 10 years. They found that wheat sensitization increased with age but it was majorly of the secondary type due to cross-reacting pollen sensitization [27].

## CONCLUSION

Our study reveals that one in three allergic children in our clinic had wheat sensitization. These children also had other food and aeroallergen sensitization with no specific organ predilection. This study could form a basis for future comparison over time of wheat sensitization in children in the region.

**Competing Interests**

The author declares that there are no competing interests.

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