

Original Article

Sensitizations to wheat and strawberry: are they a tangible threat to atopic Egyptian

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Abstract: Background: definite figures of allergy to wheat and strawberries in Egypt are lacking. We investigated IgE-mediated sensitization to wheat and strawberry among a group of allergic children, and the relation between wheat and strawberry sensitization. Patients and Methods: This study comprised 256 children, with physician-diagnosed allergy: bronchial asthma (98 patients), allergic rhinitis (28 patients), atopic dermatitis (53 patients) and food allergy (10 patients). Sensitization to wheat and strawberry was assessed using prick testing, followed by oral challenge test to prove allergy. Results: Wheat sensitization was observed in 9.4% of the studied children with confirmed allergy in 0.4%. Strawberry sensitization was observed in 7.8% of patients, with 2% confirmed allergy. Either sensitization did not influence response of allergy to treatment. Wheat and strawberry sensitizations were positively correlated. Conclusion: Wheat and strawberry allergies are not common among Egyptian children with allergic disorders; and did not impact the response to allergy treatment.

Keywords: Food allergy, wheat allergy, strawberry allergy, allergic children

Introduction

IgE-mediated food allergy (FA) is a worldwide health problem that affects almost 30% of the population and hinders numerous aspects of life [1]. Up to 60% of the world people exhibit IgE-mediated sensitization against protein antigens [1]. FA can lead to a niche of manifestations which can be, in some occasions, severe life-threatening such as anaphylaxis, or more chronic like atopic dermatitis (AD), gastrointestinal illness and/or allergic airway disease [2]. Incidence rate of FA has increased over the past three decades, with a worldwide increase in the prevalence of FA up to 3.5-8% in children [3]. IgE-mediated FA risks the patients to continue suffering from allergy till adulthood [3]. Interestingly, in IgE-mediated FA, the spectrum of allergy manifestations is not necessarily related to the number of the culprit allergens [2]. Cross-reactivity was proved among certain allergens sharing the same antigenic protein such as allergy to different tree nuts; another trick of FA mediated by IgE sensitization [2].

Wheat is an increasingly recognized trigger for FA, both IgE and non-IgE mediated. Regarding

IgE-mediated wheat allergy (WA), AD is the most common presenting symptom, followed by asthma and allergic rhinitis (AR); however, anaphylaxis can be infrequently observed [4]. WA prevails chiefly in children with a family history of atopy [5]. IgE-mediated WA is common in westernized countries, affecting 0.4 to 1% of children [6]. On the contrary, it has lower rates of prevalence in Asia, with the exception of Japan and Korea [7]. The precise diagnosis of WA still relies on standardized challenges which must be done under medical supervision. Early introduction of wheat might reduce the risk of wheat sensitization early in life, but it does not affect the risk of developing WA [8].

Fruits from the Rosaceae family are frequently allergenic in the Mediterranean area [9]. Strawberry, belonging to the Rosoideae subfamily, has an apparently unjustified reputation among the general population with common self-reported symptoms [10]. Strawberries can elicit allergic responses in atopic patients through three different components: Fra a 1, Fra a 3, and Fra a 4 [11]. Allergy to Fra a 1 is more common in Central and Northern Europe, while Fra a 3 and 4 are more prevalent in the

Sensitizations to wheat and strawberry in children

Mediterranean area [12]. Strawberry allergy is generally mild, in the form of IgE-mediated pollen-food allergy syndrome. Allergic patients present with oral and circumoral itching and swelling, but also may suffer from gastrointestinal and/or respiratory manifestations, and in rare instances, they may present with anaphylaxis [13].

Diagnosing IgE-mediated FA sensitization can be achieved through in vivo (skin sensitization test) or in vitro (serum specific IgE levels) testing guided by the history of exposures. However, confirmation of allergy requires oral food challenge (OFC) testing by a well-trained allergist [2, 13]. Complete avoidance of the causative allergens is not any more recommended with few exceptions, rather, stepwise approach of oral challenge is preferred and oral immunotherapy is in situations in which benefit would outgrow the risk [13].

We aimed to investigate IgE-mediated allergy to wheat and strawberry among a group of atopic children in relation to their clinical parameters, and to explore a possible relation between wheat and strawberry sensitization. We chose to study children suffering from different forms of allergy to evaluate if there is certain predilection of wheat or strawberry sensitization towards any form of allergy.

Materials and methods

A cross-sectional study was designed, and patients were recruited from Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Ain Shams University, Cairo, Egypt. Study population: A total of 256 children with physician-diagnosed allergy were consecutively enrolled after illustrating and obtaining verbal consent from their caregivers. Allergy diagnoses were distributed as follows: 98 patients with asthma, 28 with allergic rhinitis (AR), 53 with atopic dermatitis (AD), 10 with food allergy (FA), and 67 with combined allergies. The study protocol gained approval from the local Research Ethics Committee of the Department of Pediatrics, Ain Shams University.

Inclusion criteria: (all should be fulfilled)

- Age between 1 and 18 years.
- Atopic patients: verified by previous positive skin prick test (SPT) to any environmental allergen such as molds, pollens or grass.

- Physician-diagnosed allergic disease: asthma diagnosed according to the Global Initiative of Asthma (GINA) 2018 update [14], AR diagnosis followed the Allergic Rhinitis and its Impact on Asthma (ARIA), 2018 criteria [15], and FA diagnosed according to the National Institute for Health and Care Excellence (NICE), 2016 [16].

Exclusion criteria

- Inability to stop antihistamine therapy for 1 week before performing SPT.
- Dermographism or severe eczema.

Study tools and methods

All patients were subjected to the following

- Clinical evaluation including age, gender, residence, family history of allergy, age of onset of allergy symptoms, possible triggering factors, frequency of flare ups, treatment modality, and adherence and response to treatment.
- Skin sensitization testing: it was used as an indicator for the status of IgE-mediated sensitization. SPT was done using wheat flour extract, and Prick-prick test (PPT) using the raw fruit was done to assess wheat and strawberry sensitization respectively. Histamine dihydrochloride (10 mg/ml, equivalent to 6 mg histamine) and saline were used as positive and negative control respectively (Extracts were obtained from Omega, Canada - Allergy Overseas Consultants Inc., 82 Toor St, Port Said, Egypt).

Preparations: The test was performed and interpreted by the investigator in the integrated laboratory of the Pediatric Allergy, Immunology and Rheumatology Unit, taking into consideration all the pretest precautions and after test care. Precautions against anaphylaxis were secured. H1 antihistamines were discontinued at least 1 week earlier. The maneuver was explained to caregivers prior to testing.

Procedure: The test was performed in the forearm volar aspect through good exposure and sanitation, followed by marking the sites for skin pricks then applying a drop of each reagent on its specific site (being at least 5 cm apart from each other). Gentle pricking of the skin with special lancets was done by the trained investigator.

Sensitizations to wheat and strawberry in children

Table 1. Demographic data and allergy distribution in the studied children

		Total no.=256
Gender	Females	117 (45.7%)
	Males	139 (54.3%)
Age at time of enrollment (years)	Median (IQR)	7 (4-9)
	Range	1-15
Age at diagnosis (years)	Median (IQR)	3 (2-4.5)
	Range	0.42-12
Diagnosis	Asthma	98 (38.3%)
	AR	28 (10.9%)
	AD	53 (20.7%)
	FA	10 (3.9%)
	Combined	67 (26.2%)
Family history of allergy	No	78 (30.5%)
	Yes	178 (69.5%)

AD: atopic dermatitis, AR: allergic rhinitis, BA: bronchial asthma, FA: food allergy, IQR: interquartile range, No.: number.

Test Interpretation: The result was read after 15-20 minutes. Wheals were carefully measured. The diameter of the wheal, using a transparent mm-marked ruler was recorded. A diameter <3 mm was considered as negative and diameters equal 3 mm or more denoted sensitization [15].

- **Oral food challenge (OFC):** OFC is the gold standard test for allergy confirmation. Sensitized patients underwent open OFC, to diagnose WA and/or strawberry allergy done by the investigator inside the hospital, considering all the required precautions. In case of wheat sensitization, the patient was given whole wheat starting from small doses (1-50 mg) followed by increasingly larger hourly doses ending with a cumulative dose of up to 0.5-1 g of wheat protein. Same procedure was followed for strawberry sensitized children. Appearance of any mucocutaneous, respiratory, gastrointestinal or vital changes during the duration of the test was sufficient to stop the procedure and consider the patient as allergic.

Statistical analysis

Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Quantitative variables were reported as median and interquartile. Categorical data were presented as number and percent. Probability *p* values <0.05 was considered significant in comparative and correlative statistics.

Results

Description of the study population

The 256 studied children were 45.7% females and 54.3% males (female to male ratio=1:1.2) with median (IQR) age of 7 (4-9) years. The median (IQR) age at time of diagnosis of allergy was 3 (2-4.5) years. Allergy distribution among the studied children was as follows: asthma in 38.3%, allergic rhinitis (AR) in 10.9%, atopic dermatitis (AD) in 20.7%, food allergy (FA) in 3.9%, and combined allergies in 65%; the most prevalent combination was AR and asthma. Family history of allergy was positive in 69.5% of cases (**Table 1**).

Wheat and strawberry sensitization and allergy

Based on history, wheat allergy (WA) was suspected in 3 patients and strawberry allergy in 7 other patients. According to the results of SPT, wheat sensitization was detected in 9.4% of all the patients (none had a history suggestive of WA). WA was confirmed through OCT in only one patient (0.4%). Sensitization to strawberry was found in 7.8% of the children. Confirmed allergy was found in 2% of sensitized patients (**Figure 1**). There was statistically significant association of wheat and strawberry sensitization (Chi Square test value: 10.862, *P* value: 0.001).

Wheat sensitization was observed more frequently in patients with AD, although this was statistically insignificant. Meanwhile, strawberry sensitization was significantly more prevalent in patients suffering from AD and combined forms of allergy (**Figure 2**).

Patients' sensitization to wheat had significantly younger age at onset of their allergic disease compared to their non-sensitized peers. The response to treatment of the allergic disease was comparable in both wheat sensitized and non-sensitized patients (**Table 2**). Similarly, strawberry sensitized patients had lower mean age, however, sensitization did not impact the response of allergy to treatment (**Table 3**).

Discussion

Allergy to either wheat or strawberry was assumed by many patients/legal guardians as being responsible for the allergic manifesta-

Sensitizations to wheat and strawberry in children

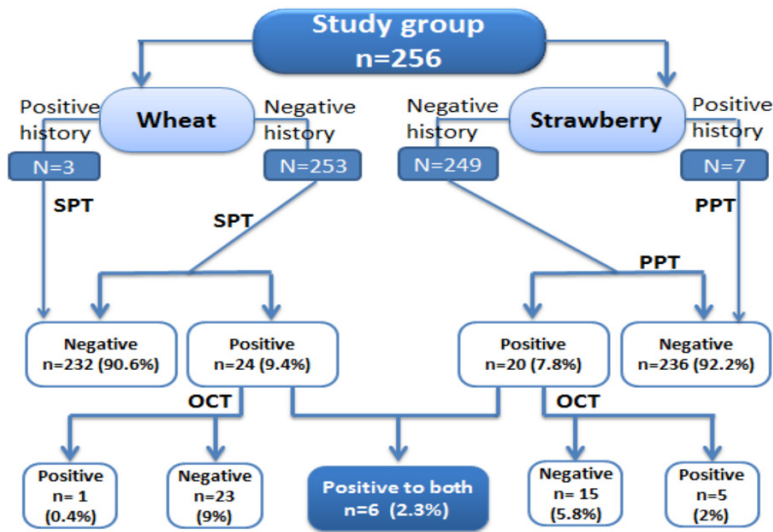


Figure 1. History, sensitization and allergy to wheat and strawberry among the studied children.

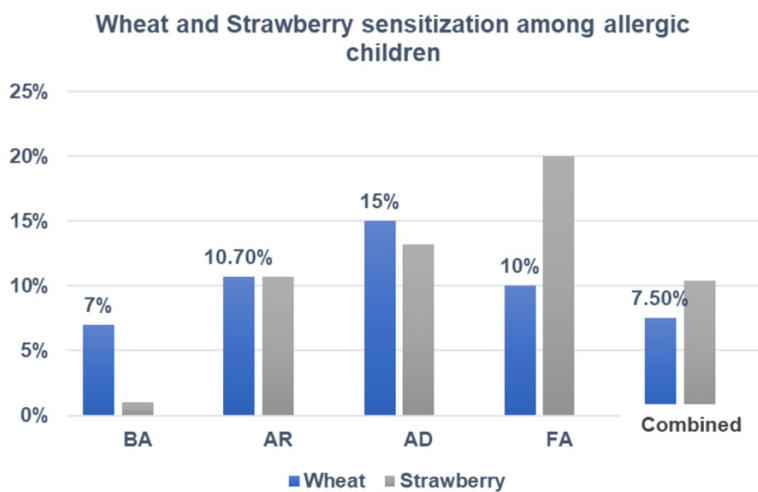


Figure 2. Wheat and Strawberry sensitization distribution among different forms of allergy.

tions. In this work, we found that IgE-mediated sensitization to wheat and/or strawberry was limited. Surprisingly, patients who were detected to be sensitized to either wheat or strawberry did not suspect any of the tested food stuff. Wheat sensitization was detected in 9.4% of patients and only one patient had confirmed WA. Thus, the frequency of WA among our studied children was 0.4% (1/256). This frequency matches the western prevalence rates of WA among children [17-20]. Therefore, sensitized patients are not necessarily allergic to wheat and WA is not as common among allergic chil-

dren as thought. Nevertheless, geographical variations, age of first exposure, and environmental factors can change the sensitization map worldwide [21], such as in Thailand where WA was reported in 70% of toddlers [22].

Sensitization to wheat without causing allergic symptoms was reported by many authors [17, 23-25]. Wheat tolerance in sensitized people was described [17, 26, 27], given the probable cross antigenicity between wheat and pollens, particularly grass pollen allergy [5, 25, 28].

Oral challenge test (OCT) was a challenge in the sensitized patients to confirm being allergic, knowing the possibility of wheat induced anaphylaxis during the test [29-31]. Fortunately, none of our tested patients developed anaphylaxis. One patient was found truly allergic to wheat. Interestingly, WA was not included among the commonly detected food allergens in allergic children, not only in Egypt [32, 33], but also in other different geographical areas [10, 34, 35]. Therefore, confirmation of WA through OCT would be mandatory to avoid unnecessary precau-

tions for the sensitized children without evidence of allergy.

Although we were limited by the uneven age distribution of allergic children, it was noticeable that wheat sensitization was more prevalent in children aged between 3 and 7 years. This might participate to the less detectable WA among the studied patients because children typically outgrow their allergy when they get older [25-27, 36]. Thereby, we were not able in this series to draw conclusions regarding the age of WA manifestations and tolerance.

Sensitizations to wheat and strawberry in children

Table 2. Demographic data, in relation to wheat sensitization

		Wheat sensitization		Test value	P-value
		Negative (232)	Positive (24)		
Gender	Females	105 (45.3%)	12 (50%)	0.2*	0.657
	Males	127 (54.7%)	12 (50%)		
Current age (years)	Median (IQR)	7 (4-9)	5 (3-7)	-2.16 \neq	0.031
	Range	1.5-15	1-13		
Age at diagnosis (years)	Median (IQR)	3 (2-5)	2 (1-3)	-2.29 \neq	0.022
	Range	0.42-12	0.5-10		
Family history	No	69 (29.7%)	9 (37.5%)	0.62*	0.432
	Yes	163 (70.3%)	15 (62.5%)		
Response to treatment	Poor	3 (1.3%)	0 (0%)	0.31*	0.575
	Good	229 (98.7%)	24 (100%)		

*: Chi-square test; \neq : Kruskal-Wallis test.

Table 3. Demographic data in relation to strawberry sensitization

		Strawberry sensitization		Test value	P-value
		Negative (236)	Positive (20)		
Gender	Females	106 (44.9%)	11 (55%)	0.76*	0.385
	Males	130 (55.1%)	9 (45%)		
Age (years)	Median (IQR)	7 (4-9.5)	5 (3-6)	-2.68 \neq	0.007
	Range	1-15	2-11		
Age at diagnosis (years)	Median (IQR)	3 (2-5)	1.5 (1-2)	-3.06 \neq	0.002
	Range	0.42-12	1-10		
Family history	No	73 (30.9%)	5 (25%)	0.31*	0.580
	Yes	163 (69.1%)	15 (75%)		
Response to TTT	Not improved	3 (1.3%)	0 (0%)	0.26*	0.612
	Improved	233 (98.7%)	20 (100%)		

*: Chi-square test; \neq : Kruskal-Wallis test.

Wheat sensitization was more prevalent among children with AD, followed by those with AR. Nevertheless, that sensitization was insignificantly correlated to the response of AD or AR to treatment. Concomitant wheat sensitization with AD was a common finding in literature without a logistic explanation [5, 35, 37].

In this series, we were stimulated to study the sensitization to strawberry correspondingly to sensitization to wheat in allergic children because of the theoretical risk of cross reactivity between strawberry and wheat due to agricultural considerations. Furthermore, both food stuffs were claimed by many caregivers to be responsible for their children's allergies in Egypt. The theory was provoked as strawberry was recommended to be cultivated on wheat straw beds. Additionally, many fruits' processing conditions may induce alteration of immu-

ne-reactive epitopes on allergenic proteins, destroying existing epitopes and generating new ones (formation of neo allergens), leading to unexplained cross reactivities [38]. Indeed, we found a positive correlation between wheat and strawberry sensitization, but not allergy. Combined allergy can not be denied particularly that we detected only one patient with WA.

Strawberry sensitization was elicited in 7.8% of the studied children, whereas confirmed allergy was detected in 5/256 (2%) of patients. Actually, the number of patients who recalled allergic symptoms upon exposure to strawberry was 7, more than those who had confirmed IgE-mediated allergy. This observation is in agreement with Patiwael and colleagues, whereas, strawberry sensitization using prick test was lower than the number of strawberry-allergic patients [39]. The aforementioned observation

Sensitizations to wheat and strawberry in children

raises the possibility of the presence of non-IgE mediated strawberry allergy, leaving a space for more research to study the exact extent of the fruit's allergy. Strawberry sensitization was more detectable in patients suffering from FA (FA was diagnosed using SPT followed by elimination and challenge test) followed by those with AD. Unlike wheat, sensitization to strawberry was evident in allergic children from different countries such as Egyptian [33], Portuguese [10] and Spanish children [34], whereas strawberry was considered among the commonly implicated foods in allergy. Strawberry sensitization and allergy was not correlated to the severity of allergic manifestations or response to treatment.

Although insignificant, asthmatic patients were more sensitized to wheat than strawberry. On the contrary, patients with food allergy (FA) were more sensitized to strawberry compared to wheat. The real impact of these findings on the allergic manifestations and progression of the disease is to be further studied.

This study has some limitations as we did not explore the non-IgE mediated WA especially in patients with suggestive history. The age groups of the enrolled patients were not evenly distributed; thus, we could have underestimated the prevalence of either wheat or strawberry sensitization or allergy, which may be more commonly detected in certain age groups. A prospective cohort study will provide a better understanding of the age-related prevalence of WA and the age at tolerance development.

In conclusion, confirmed allergy to either wheat and strawberry was not common among Egyptian allergic children, detected in 0.4% and 2% of the studied children. Although wheat and strawberry sensitizations were significantly correlated, both did not affect the control of allergic manifestations. More research is recommended to determine the real-life impact of combined or cross-reactive wheat-strawberry sensitization on symptoms and severity of allergy, particularly AD.

Disclosure of conflict of interest

None.

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Sensitizations to wheat and strawberry in children

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Sensitizations to wheat and strawberry in children

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