

Original article

Patterns of sensitization to food allergens among allergic adults and children following-up in Zagazig university hospitals, Egypt

Background: Data regarding food sensitization and food allergy in developing countries are lacking. We sought to explore the frequency and pattern of sensitization to food allergens among a sample of Egyptian allergic patients. **Methods:** This cross-sectional study included 1373 allergic patients. They were subjected to thorough history taking, skin prick test, serum specific IgE (sIgE) level. Patients with evidence of sensitization to food were subjected to food elimination followed by an open oral food challenge (OFC) test. **Results:** Four-hundreds and nineteen patients (30.5%) (76 children and 343 adults) had evidence of sensitization to one or more food allergen. Among children, 41 (52.5%) had urticaria, 31 (39.7%) allergic rhinitis, 13 (16.6%) pollen food allergy syndrome, 16 (20.5%) bronchial asthma, 9 (11.5%) eczema and 7 (9%) had GIT symptoms. Among adults, 152 (44.5%) had allergic rhinitis, 149 (43.6%) urticaria and 57 (16.7%) had GIT symptoms. The most common allergens among children were peanut (31; 39.7%), fish (29; 37%), egg (18; 23%), and strawberry (17; 21.79%) while in adult, they were jalapeno pepper (123; 36%), egg (122; 35.7%), tomato (120; 35.1%), peanut (110; 32.2%), and fish (109; 31.9%). Significant associations were found between sensitization to different types of foods including associations between citrus fruits and mango, and between shrimps and crabs ($p<0.001$). Out of the sensitized 419 patients, 118 (28.2%) had positive OFC test. **Conclusion:** A significant proportion of both adults and children with allergic disorders are sensitized to foods. Pepper, peanut, egg, fish, tomato, strawberry are the most common foods to which Egyptian patients are sensitized.

Keywords: Food allergens, adults, children, allergy.

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INTRODUCTION

It was thought that food allergy (FA) in the developing world was rare, but emerging epidemiological data have shown otherwise in the recent decade. This could be attributed to the previous under-recognition or underreporting of FA prevalence.¹ Indeed, the health burden of food allergy is anticipated to rise substantially in the next decade.²

Food allergy present in different forms, including urticaria, angioedema, exacerbation of allergic rhinitis, asthma, or atopic dermatitis.³ Food allergic patients with asthma have a higher risk of developing life-threatening food-induced reactions and an asthmatic patient with a food allergy can have higher rates of morbidity and mortality associated with asthma.⁴ The most serious consequence of food allergy is anaphylaxis.⁵

Food allergy has significant deleterious effects on family economics, social interactions, school and work attendance, and health-related quality of life. Children with multiple food allergies face many nutritional problems as a consequence of an unsupervised elimination diet, which may lead to failure to thrive.⁶

There is a lack of reliable data regarding FA in most developing countries, including Egypt.^{1,6} This study aimed to uncover some aspects of IgE mediated FA among the Egyptian population. We sought to explore the frequency of food sensitization among a sample of allergic patients and determine the common sensitizing food allergens among those patients.

METHODS

This cross-sectional study included 1373 patients suffering from different forms of allergy and following-up in the Allergy and Immunology Unit,

Faculty of Medicine, Zagazig University in the period from January 2017 to June 2019. All enrolled patients were subjected to the following:

Detailed medical history taking and systemic clinical examination with special emphasis on the form of allergy, suspected triggers, symptoms and their timing, severity and control of the allergic disease, reproducibility, known risk co-factors such as exercise, non-steroidal anti-inflammatory drugs or alcohol intake, family history and coexisting medical problems.

Structured questions:

Questions were used to categorize IgE mediated allergy symptoms into: Pollen food allergy syndrome (PFAS) (pruritus and edema confined to the oral cavity associated with pollen allergy hay fever), urticaria/angioedema, allergic rhinitis/asthma, gastrointestinal (GIT) symptoms such as nausea, emesis, abdominal pain, and diarrhea after ingestion of food, atopic eczema/dermatitis and anaphylaxis triggered by food.

Food diary

Patients were also asked to keep a food diary in which they write down their daily diet and report any associated allergic manifestations, for at least two weeks.

Determination of food sensitization

Skin prick (SPT) and prick-prick tests (PPT)

Choice of food to be tested for prick-prick test was based on patient's history. The following foods were used Peanut, Egg, Fish, Tomato, Pepper, Cocoa, Strawberry, Banana, Milk, Citrus mix, Mango, Maize, Peach, Wheat, Beans, Meat, Chicken, Sesame, Shrimps and Crab. We used fresh fruit and vegetables for testing (not tinned or cooked in order not to alter allergenicity). For fruit / vegetables a lancet was pushed into a fleshy and juicy/moist site of the food then a small amount of the food substance was placed onto the skin. Then lancet was then pushed through the surface layer of the skin at a 45° angle through the food (prick-prick test). For foods like beans and wheat, they were crushed/grinded to make a paste using sterile saline, the tip of the lancet was then put in this paste and a small part of the paste was the placed on the skin before pricking through it with the lancet.⁸ Standardized saline solution and histamine dihydrochloride (10 mg/ml) were used as negative and positive controls using skin prick test (Omega diagnostic, Canada). The test was done and interpreted according to the recommendations of

the European Academy of Allergy and Clinical Immunology (EAACI).⁹

Specific Immunoglobulin E assay

The level of sIgE against various food allergens was used whenever skin prick test was contraindicated or cannot be performed, as in patients with severe asthma, severe skin allergy or those who refused to do the skin prick test. The level of sIgE was assayed using (AllergyScreen test, Germany) which is an immunoblot assay for the semi-quantitative determination of circulating allergen-specific immunoglobulin E in human serum. One reaction test detects the level of all the following allergen at once: Egg, Vanilla, cocoa, strawberry, peach, apple, strawberry, mango, milk, casein, tuna, cod fish, salmon, shrimps and crab (Panel 2A EGY).

Interpretation of the results was made according to the manufacturer's guidelines as follows: <0.35 iu/ml was classified as class 0 where allergen-specific IgE is hardly found, 0.35-0.69 iu/ml was classified as class 1 where allergen-specific IgE is Low, 0.7-3.4 iu/ml was classified as class 2 where allergen-specific IgE is significantly increased, 3.5-17.4 iu/ml was classified as class 3 , 17.5-49.99 was classified as class 4 where allergen-specific IgE is High, 50-100 iu/ml was classified as class 5, and >100 iu/ml was classified as class 6 where allergen-specific IgE is exceptionally high.

Confirmation of IgE mediated food allergy

Elimination diets

Depending on the history, SPT and sIgE, we determined which foods to be avoided. For each individually avoided food, the results of the diagnostic elimination diet should be carefully monitored and evaluated over 2-4 weeks of avoidance. Where the elimination diet leads to significant relief of symptoms, food allergy was highly suspected. Where the elimination diet does not lead to significant relief of symptoms, food allergy to the eliminated foods is highly unlikely.

Oral food challenge test (OFC):

Open OFC test was done for sensitized patients to confirm diagnosis whenever diagnosis was suspected. The test was done according to the EAACI guidelines.¹⁰ OFC was preceded by elimination of the suspected food. On the day of the test, the patient should be in a good health, chronic allergic conditions such as asthma, atopic dermatitis (eczema) and allergic rhinitis (hay fever) have to be well controlled so they do not interfere with the interpretation of any symptoms, and antihistamines have to be stopped before the OFC since they might mask mild early symptoms. Emergency treatment

such as epinephrine, antihistamines or inhaled asthma rescue medications were made available. Briefly, patients were given increasing amount of the suspected food, on interval of 25-20 min. Doubling of dose was continued until the patient reached the regular intake amount. Before each dose all the vital signs of patients were recorded and compared with the base line measures before the beginning of the test. Signs and symptoms of allergy were also observed. The test was considered positive if allergic manifestations were detected after any given dose. For patients sensitized to multiple allergens, each allergen was tested in a separate setting.

The study protocol and methodology were reviewed and approved by the hospital Ethics Committee / Institutional Review Board (IRB); approval number is 5049-6-1-2017. All adult patients and caregivers of children were asked to sign an informed written consent before enrolment in the study.

Statistical analysis

The collected data were analyzed using SPSS program (Statistical Package for Social Science) version 22.0. Numerical variables were presented as range, mean and SD or median (interquartile range) where appropriate. Categorical variables were presented as number and percentage and differences were compared using the Chi Square test. Associations between categorial variables were tested using the Chi Square test. p-values less than 0.05 were considered statistically significant.

RESULTS

Patients included in the study:

This study included a total of 1373 allergic patients who attended the allergy and Immunology Unit, Faculty of Medicine, Zagazig University. Forty percent were males (549), while 60% were females (824).

Patients with confirmed food sensitization

Out of the enrolled 1373 allergic patients, 419 (30.5%) (76 were children and 343 adults) were found to have evidence of IgE sensitization to one or more food allergen, 291 (69.5%) with skin prick test and 128 (30.5%) through serum specific IgE measurement. Regarding children, their age range was from 1 to 16 years (median=9 years, interquartile range (IQR)= 5-11.5) and for adults; age ranged from 17 to 90 years (median = 34 years, IQR= 27-45).

Clinical presentations among food-sensitized children and adults.

Out of the 419 patients with SPT or specific IgE evidence for food sensitization: 193 (46.1%) had allergic rhinitis, 180 (43%) urticaria, 85 (24%) were asthmatics, 57 (17%) pollen food allergy syndrome, 46 (11%) had eczema and 38 (9%) presented by GIT symptoms. Only one child had experienced two anaphylactic shocks induced by wheat ingestion. Among adult patients, 152 (44.5%) had allergic rhinitis, 149 (43.6%) urticaria, 57 (16.7%) oral food pollen syndrome, 58 (17%) asthma, 37 (10.8%) eczema and 31 (9%) presented by GIT symptoms. Notably, some patients had more than one form of allergic manifestations. There was no statistically significant difference in the pattern of presentation of allergy in both children and adults sensitized to food allergens. They were comparable in terms of the frequencies of allergic rhinitis, urticaria, pollen food allergy syndrome, asthma, eczema and GIT symptoms. P values were (0.77, 0.51, 0.87, 0.65, 0.96 and 0.85 respectively) (figure 1).

Food allergen to which patients were sensitized

According to the SPT and sIgE results, the most common allergen to which the adult patients were sensitized were, Jalapeno Pepper 123 (36%), Egg 122 (35.7%) followed by Tomato 120 (35.1%), Peanut 110 (32.2%), and fish 109 (31.9%). The least common were lentils 26 (7.6 %) and crab 20 (5.8 %). Among children, peanut 31(39.7%) was the most common sensitizing food allergen, followed by fish 29 (37%), egg 18 (23%), and strawberry 17 (21.79%) (figure 2). The frequency of sensitization to peanut, egg, fish, tomato, cocoa, strawberry, banana, citrus mix, mango, maize, peach, wheat, fava beans, chicken, sesame, shrimps, lentils, crab were comparable among the studied adult and children's groups with p values 0.452, 0.151, 0.620, 0.085, 0.06, 0.504, 0.506, 0.311, 0.932, 0.120, 0.276, 0.208, 0.115, 0.832, 0.060, 0.384, 0.200, 0.185, respectively. However, jalapeno pepper sensitization was more common in adults than children ($\chi^2= 7.39$, $p= 0.006$). P value could not be calculated for meat as no child showed sensitization to it. Regarding cow milk sensitization, 10 children (12.8%) showed evidence of sensitization compared to 74 adults (21.7%) but the difference between the 2 groups did not reach statistical significance ($\chi^2 =1.74$, $p=186$).

Association between different food allergens

When we tested for the association between different food allergens; several associations were found as shown in table 1.

Patients with confirmed food allergy as detected by Oral Food Challenge (OFC) test

Out of the 419 patients with evidence of food sensitization, 118 patients showed positive OFC test, 81 adults (31; 38.2% male and 50; 61.7% female) and 37 children (17; 46% male and 20; 54% female).

Adults with positive OFC were presented by Urticaria 46 (56.7%), allergic rhinitis 37 (45.6%), asthma 10 (12.3%), eczema 6 (7.4%) and GIT 3

(3.7%), while children presented with urticaria 10 (27%), allergic rhinitis 9 (24.3%), asthma 14 (37.8%), eczema 4 (10.8%) and gastrointestinal manifestations 2 (5.4%). Most common allergens detected by OFC test were Fish 46 (39%), Jalapeno Pepper 41 (34.7%), tomato 40 (33.9%), Egg 37 (31.4%), and peanut 36 (30.5%).

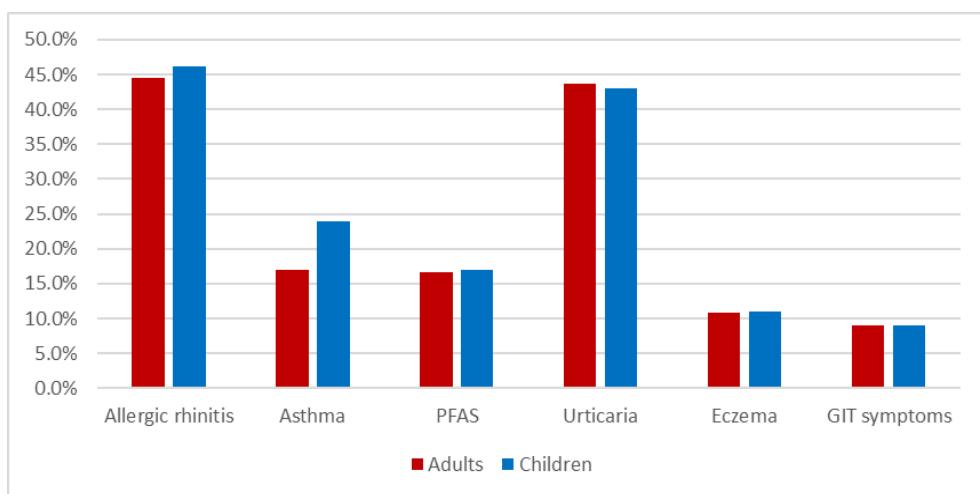


Figure 1. Allergic manifestations among enrolled adults and children with evidence of food sensitization.

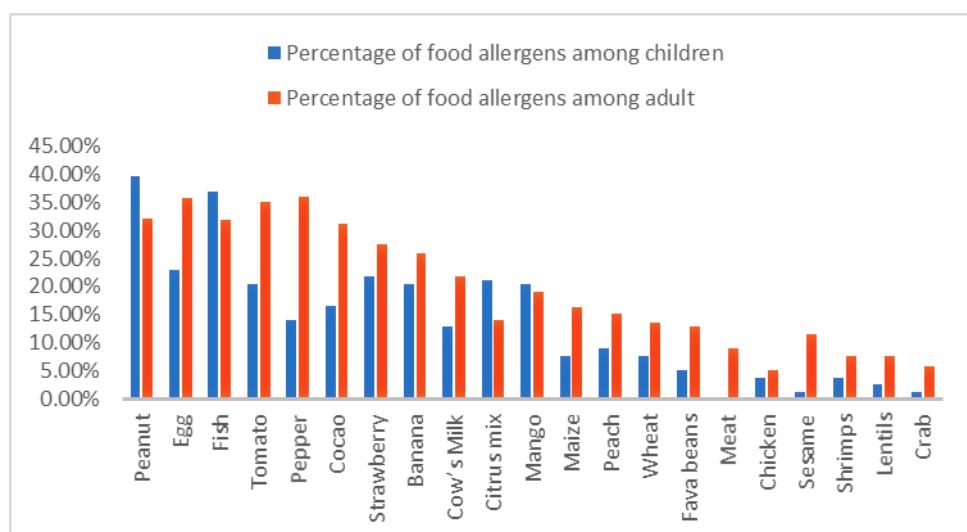


Figure 2. Frequencies of sensitization to different food allergens among enrolled allergic adults and children.

Table 2. The association between sensitization of different food allergens

Allergens (no)		Number of cases sensitized to both allergens	χ^2	p
Cocoa (120)	Wheat (54)	23	5.91	0.02*
Cocoa (120)	Peanut (141)	60	20.13	<0.001**
Peanut (141)	Tomato (136)	34	6.75	0.009**
Peanut (141)	Wheat (54)	33	20.94	<0.001**
Peanut (141)	Maize (62)	12	6.66	0.01*
Tomato (136)	Jalapeno pepper (134)	70	35.16	<0.001**
Tomato (136)	Mango (81)	44	21.89	<0.001**
Tomato (136)	Fava beans (48)	22	4.42	0.04*
Tomato (136)	Lentil (28)	17	10.93	0.001**
Citrus (83)	Mango (81)	33	27.70	<0.001**
Citrus (83)	Maize (62)	22	11.26	0.001**
Citrus (83)	Lentil (28)	13	13.39	<0.001**
Mango (81)	Maize (62)	19	5.97	0.02*
Mango (81)	Fava beans (48)	11	5.60	0.02*
Mango (81)	Lentil (28)	13	14.13	<0.001**
Strawberry (111)	Banana (105)	46	21.58	<0.001**
Strawberry (111)	Peanut (141)	21	8.29	0.004**
Peach (59)	Banana (105)	22	5.47	0.02*
Peach (59)	Maize (62)	19	16.5	<0.001**
Peach (59)	Lentil (28)	8	5.21	0.02*
Banana (105)	Fava beans (48)	19	6.09	0.01*
Maize (62)	Lentil (28)	10	10.41	0.001**
Fava beans (48)	Lentil (28)	8	8.67	0.003**
Shrimp (29)	Crab (21)	11	70.92	<0.001**

DISCUSSION

Food allergy is a global health problem in developed as well as developing countries. Data on the epidemiology and pattern of FA from most developing countries are quite limited.¹¹ This study was set to evaluate food allergen sensitization in a sample of Egyptian patients attending the Allergy and Immunology Unit, Faculty of Medicine, Zagazig University, Egypt.

Around one third (30.5%) of the 1373 allergic patient included in the study was found to be sensitized to one or more food allergen. Results of this study show that the most common allergen to which the adult patients were sensitized were, Jalapeno Pepper 123 (36%), Egg 122 (35.7%) followed by Tomato 120 (35.1%), Peanut 110 (32.2%), and fish 109 (31.9%). The least common were lentils 26 (7.6 %) and crab 20 (5.8 %). Among children, peanut 31(39.7%) was the most common sensitizing food allergen, followed by fish 29 (37%), egg 18 (23%), and strawberry 17 (21.79%). Food sensitization was commonly reported in allergic patients in several studies. In Saudi Arabia, a cross-sectional study, carried out on 1341 children and adults with bronchial asthma attending King Abdulaziz University Hospital, found that the prevalence of clinical sensitivity to

food allergies was 29%.¹² Also, in a study done in Islamabad (Pakistan), out of 689 patients suffering from allergic diseases, sensitization to food allergens was found in 270 (39.2%).¹³ Other studies reported 32–35% and 41.7 % sensitization to various food allergens in allergic patients from India¹⁴ and Hungary¹⁵ respectively, the results from different studies in different parts of the world are comparable to our findings, reflecting the significant role that food allergens might play in allergic disorders.

Regarding our results, 419 (30.5%), of which 76 were children and 343 adults, were sensitized to food allergens. In another Asian study included 435 patients, 213 children, and 222 adults, the percentage of sensitization to food allergen among allergic patients in children was 54%, meanwhile it was only 13% in adults.¹⁶ The lower frequency of food sensitized children among our patients in comparison to other studies may be attributed to the age factor, as the children in our study had median age of 9 with IQR: 5.5-11 years, whereas food allergy most often occurs in children aged up to three years.¹⁷ Difference in the prevalence of food allergy and food allergy sensitization might be also affected by other different factors, including ethnicity (increased in Black and Asian children

compared with White children), composition of the microbiome, obesity and the timing and route of first exposure to foods. Additionally, differences in HLA and other genes, feeding habits including vitamin D insufficiency, reduced consumption of omega-3 and antioxidants, and increased use of antacids have been related to variability in prevalence.¹¹

Among our patients with evidence of sensitization to food, urticaria was the most common form of allergy in adults (46; 56.7%) while asthma was the most common form in children (14; 37.8%), patients from both groups were also presented by rhinitis, eczema and GIT symptoms. This variety in the manifestations of food allergy may be due to difference in the individual susceptibility and exposure to different environmental factors based on age and different geographical regions and cultures.²⁰

Pollen-food allergy syndrome (PFAS) occurs in susceptible patients with allergic rhinitis when they eat food with allergens that belong to the plant family Rosaceae, which includes apple, pear and peach. PFAS is most common in birch-allergic patients.²¹ In our study, 57 (17%) adult patient and 13 (16.6%) child had evidence of PFAS; all these patients initially suffered from allergic rhinitis. The most common reported foods were tomato, pepper, peanut, and peach, while the most common incriminated pollens in our study were birch and timothy grass. In Korea, the prevalence of PFAS in children was as high as 42.7%²² and in Swedish children it was 25%.²³ On the contrary, in Mexico, the prevalence of PFAS among children with pollen allergy was around 9.6–12.2%.²⁴ It should be noted that adults show higher prevalence of PFAS than children, as it is well established that the prevalence of PAFS increases with age, children usually do not develop allergic rhinitis until 3 years old.²⁵

Among our studied group, only one patient showed an anaphylactic reaction after wheat ingestion, which is considered a lower rate compared with other countries. For example, in Australia it was 10.3 and 4.3 per 100 000 for adults of 15–29 years, and >30 years, respectively.²⁶ In the UK, hospital admission due to food anaphylaxis had a rate of 0.09 per 1000 person.²⁷ In a study included multiple ethnic groups in New Zealand, found that the average annual rate of hospital food-induced anaphylaxis was 4.8 per 100 000 adults (aged ≥15 years). The rate of anaphylaxis revealed significant differences by gender, age group, and ethnicity. Seafood represented the principal culprit causing food allergy anaphylaxis, followed by nuts.²⁸ Low representation of anaphylaxis in our

study might reflect under recognition of cases whether due to lack of seeking medical advice by patients or their caregivers, lack of awareness of physicians or inadequate allergists in the region.

In our study, jalapeno pepper, egg, tomato, peanut and fish were the most common sensitizing allergens among adult patients. The least common were lentils and crab. Among children, peanut 39.7% was the most common allergen, then fish 37%, egg 23%, and strawberry 21.79%. No statistically significant difference has been detected except in Jalapeno pepper, which is more common in adults than children. Cow milk protein allergy is not common among children in this study, as the median age of children in this study is 9 years old, while the highest prevalence of cow milk protein allergy is in the first year of life, afterward, tolerance to cow milk gradually develops with age in most patients.²⁹

In 2012, a survey by World Allergy Organization (WAO) was performed to collect information on the global patterns and prevalence of food allergy in children. Results have shown that in children less than 5 years, allergens generally including cow's milk, egg, peanuts and seafood, with regional variations in the relative frequency. However, in older children (>5 years), peanuts, tree nuts, seafood, egg and milk tend to be common in most regions. It was noted that these studies were based on clinical experience and symptoms.² In a previous study on Egyptian asthmatic children, the most common incriminated sensitizing food allergen were fish, milk, egg, and wheat.³⁰ Another study by Hossny et al. concerning peanut allergy in Egyptian children with asthma, reported that 7% of their studied patients were sensitized to peanuts.³¹ Across the gulf countries, allergies to fish, shellfish, eggs, cow's milk, fruit, vegetables, peanuts and tree nuts were found to be associated with allergic manifestations.^{12,32,33} In Morocco, eggs, peanuts, wheat flour³⁴ and Fish (2.5%) were mostly incriminated.³⁵ Different results between studies can be attributed to several factors including age factor, different panel of food allergens tested, the use of different forms of extracts with wide variety of preparations, variations in the equipment used in SPT/PPT, and sIgE test kits used, in addition to the inclusion of different forms of allergy -not only asthma- in our study.

Distinct regions in the world revealed specific patterns for food sensitization. One study that included Asian population with allergic rhinitis, found that the top children food allergens were egg white (54%), milk (31%) and soya bean (13%); rates that were significantly higher than those in

adults of the same region.¹⁶ Allergy to cow's milk was the second most common immediate-type food hypersensitivity in Japanese children.³⁶ Across Europe, profiles in northern countries like Russia, Estonia, and Lithuania, showed that citrus fruits, chocolate, honey, apple, hazelnut, strawberry, fish, tomato, egg, and milk were the most common sensitizing food allergens. On the other hand, in Sweden and Denmark, birch pollen (BP) -related foods such as nuts, apple, pear, kiwi, stone fruits, and carrot were the most frequent. Thirty-two percent of the patients reported symptoms to chocolate, and 15% to Cocoa.³⁷

A remarkable finding was revealed when comparing allergen profile in our study, with other studies; where in our study, jalapeno pepper and tomato allergens which were the top sensitizing food allergens, yet, they had not occupied this front position among other populations. However, the importance of tomato in the induction of food allergy had been shown in Italians as well, where the most frequent culprit foods were tomato, cereals, and peanut.³⁸ This may be due to similar food habits as tomato is an essential ingredient in both the Egyptian and Italian cuisine. Additionally, the geographic proximity of the two Mediterranean countries may yield the same plant cultivars. Different tomato cultivars contain different levels of Bet v 1-related allergen in tomato fruits.³⁹

In our study, 20.5% of children and 19% of adults were sensitized to mango. Profilin from mango is structurally like birch tree profiling and is responsible for cross-reactions between mango and peach, pear, and apple.⁴⁰ This may explain the association found between mango allergy from one side and citrus and tomato allergy from the other side.

Although our study did not include allergen component resolved diagnosis (CRD) to determine sIgE against purified native and recombinant allergenic molecule to which patients are sensitized or cross react, significant associations were detected between peanuts and coca, maize and fish, crab and shrimp, lentil and crab, wheat and peanuts, pepper and tomatoes, mango and tomatoes, lentil and tomatoes, mango and citrus, maize and citrus, meat and citrus, lentil and citrus, lentil and mango, banana and strawberry, milk and egg, maize and peach, meat and maize, lentil and maize. These associations are probably due to the occurrence of the same protein groups in different plants.

In our study, food sensitization was found in 419 patients by either skin prick test or sIgE detection serum, however only 118 (28%) were confirmed to

have food allergy as detected by OFC test. Although both skin prick test and sIgE detection in serum, have good sensitivity, yet their positive results indicate food sensitization and not necessarily allergy, except in some cases where results are highly positive. This demonstrates that although the food challenge test is a time-consuming test, requires considerable effort and experience, and carries the risk of severe reactions, yet, it is essential for accurate diagnosis.^{9,41} Allergists must always consider that diagnosis of food allergy would be followed by food elimination which implies a substantial constraint on the quality of life, cost of living and causes nutritional deficiencies which is critical in adults and typically more in pediatric population, so diagnosis of food allergy should be as accurate as possible.

CONCLUSION

Food allergy is common and responsible for a substantial load of manifestations in the studied allergic population. The Egyptian profile of allergic foods is unique. Further studies involving CRDs of different allergens and the protein content of the Egyptian cultivars are needed to be conducted to provide better understanding of Egyptian food allergy patterns. Our study is limited by availability of detection of CRDs which would provide more accurate diagnosis for food sensitization and thus decreases the load of performing OFC test. Studies considering epidemiology of such disorder should include a sample size large enough to represent the whole population to get sound information regarding food allergy among the Egyptian population.

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