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Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Food sensitization in preschool Egyptian children with recurrent wheezing

Alameldin Mohamed Abdallah[1], Naglaa S. Osman[1], Hanaa A. Mohammad[1], Kotb A. Metwalley[1], Mostafa Embaby[1] and Tarek T. ElMelegy[2]

BACKGROUND: Food allergy is common in children with prevalence up to 10%. We assessed the clinico-laboratory characteristics and frequency of food sensitization to the commonly consumed food among upper Egyptian preschool children with recurrent wheezy chest.

METHODS: This cross-sectional descriptive study was conducted on 100 preschool children with recurrent wheezy chest recruited from Emergency, Allergy, and Pulmonology units, Assiut University Children's Hospital, Egypt. All enrolled patients were subjected to history taking, through examination, chest X-ray, skin prick testing (SPT), and lab investigations.

RESULTS: Family history of allergy was found in 66 patients, while history of other allergies was reported in 47 patients. History of food allergy was positive in 47% of the studied patients, and 28 patients had positive reaction by SPT. Sensitization to fish, milk, egg, and wheat was found in 15, 8, 5, and 4 patients, respectively. Eighteen out of the 28 patients who were sensitized by SPT gave positive history of food allergy, while ten patients had no suggestive history; also, history suggestive of food allergy was negative in 35.7% of sensitized patients versus 61.1% of non-sensitized patients.

CONCLUSIONS: Food sensitization is common in preschool Egyptian children with recurrent wheezing.

Pediatric Research (2020) 88:580–586; https://doi.org/10.1038/s41390-020-0960-0

IMPACT:

- Food sensitization is common in children with prevalence up to 10%, and in atopic children up to 30%.
- Sensitization to fish was the most common type of sensitization observed among preschool children with recurrent wheezing, followed by milk, eggs, and wheat, respectively.
- SPT aided by history is a good screening tool to determine whether patients need to avoid some foods that can cause allergy in order to help in controlling their symptoms.

INTRODUCTION

Recurrent wheezing is one of the most common chronic diseases in the world, resulting in a substantial worldwide burden of disease. The answer of the question why recurrent wheezy chest prevalence is recently increasing has not been definitely known, which limits the opportunities to develop targeted primary preventive measures.[1]

Recurrent wheezing is one of the long-term childhood conditions, and ~9% of children are affected by it.[2] Its prevalence varies in different countries ranging from 1 to 18%. More than seven million children in the United States of America are affected, and 50–80% of them develop their symptoms before their fifth birthday.[3]

The most significant burden of recurrent wheezing increase is noted among children between 1 and 5 years of age. In this young age, it is difficult to diagnose asthma, as, among other things, pulmonary function tests cannot be performed reliably before the age of 6 years, and in this age, wheezing remains one of the main symptoms of asthma, although it is not clear whether young children who wheeze will develop asthma or not.[4]

Food allergy is common in children with prevalence up to 10%, and in atopic children up to 30%.[5] Food allergy is thought to be increasing in prevalence by almost 50% over the past two decades in countries with a Western lifestyle.[6]

The relation between food allergy and asthma or recurrent wheezing remains under-recognized, particularly when the causative food is consumed regularly in children, such as cow's milk; however, it has been shown that sensitization and clinical allergy to food are more common in patients with asthma than in those without asthma. Nevertheless, food allergy is rarely thought of in routine evaluation of patients with asthma or wheezy chest.[7]

The aim of this study is to assess the clinico-laboratory characteristics and frequency of food sensitization to the commonly consumed food in preschool children with recurrent wheezing among Upper Egyptian children.

PATIENTS AND METHODS

Study design and patients

This cross-sectional descriptive study was carried out on 100 preschool children with recurrent wheezy chest recruited from

[1]Pediatric Department, Faculty of Medicine, Assiut University, 71526 Assiut, Egypt and [2]Clinical Pathology Department, Faculty of Medicine, Assiut University, 71526 Assiut, Egypt
Correspondence: Alameldin Mohamed Abdallah (Alameldin17@gmail.com)

Received: 22 January 2020 Revised: 27 March 2020 Accepted: 24 April 2020
Published online: 2 June 2020

Emergency, Allergy, and Pulmonology units in Assiut University Children's Hospital, Egypt.

Inclusion and exclusion criteria

Children of both sexes, aged 2–5 years, with at least three episodes of wheezy chest, cough, and difficult breathing in the year preceding the study showed improvement with inhaled short-acting β2 agonist; thus, according to GINA guidelines they could be considered as having asthma.[8] Children with extensive skin lesions and positive dermatographism, pneumonia, chronic respiratory diseases, or any other chronic central nervous system, hepatic, metabolic, or renal diseases were excluded from the study.

Methodology

All enrolled patients were subjected to history taking, through examination, chest X-ray, skin prick testing (SPT) to commonly consumed food (cow's milk–egg–fish–wheat) and lab investigations (complete blood count (CBC) and serum immunoglobulin E (sIgE)).

History included description of the wheezy episodes in the past year and if the episodes were episodic or has multiple triggers, family history of allergy, the possible precipitating factors for wheezy episodes, and the level of asthma control according to GINA 2018.[8] It also included any previous allergic reaction to food and any other food excluded from the diet without history of previous reaction to it. Also, it included type of feeding in the first 4 months (e.g., exclusive breast feeding or mixed feeding and its duration), time of weaning and type of weaned food, are some of the children born preterm, and is there a history of bronchiolitis?

SPT was performed using commercial allergen extract food kit (Allergy Therapeutics, Worthing, England) that contained six vials with a dropper, one for histamine hydrochloride 1% (positive control), one for phenolated glycerol-saline (negative control), and one for each of cow's milk, egg, cod fish, and wheat, the commonly consumed food by the Egyptian preschool children. Antihistamines if used were stopped 1 week before the test. Epinephrine ampoule was ready for any possible systemic reactions. The test sites on the back were marked at least 3 cm apart to avoid the overlapping of positive reactions. The marked sites were dropped by the allergen and gently pricked by sterile lancet.[9]

The results were interpreted after 15–20 min. The resultant wheal and flare were measured in millimeters using a ruler. A successful immunological reaction was defined when the saline control was negative, and histamine had a diameter ≥3 mm. The skin test reaction to any of the allergens was considered positive if the diameter of the wheal was ≥3 mm, while a wheal diameter <3 mm was defined as a negative response.[10]

In addition, 5 ml of venous blood was collected from each patient by aseptic technique into an EDTA tube (2 ml; for CBC) and into a plain Wassermann's tube (3 ml). Plain tubes were placed in the water bath (37 °C) for 15 min and sera were separated by centrifugation at 3000 r.p.m. for 15 min and the following investigations were done:

- CBC.
- Serum total IgE level was measured using VIDAS Total IgE test kits (cat. no. 30419).

Statistical analysis

Data entry and statistical analysis were performed using SPSS version 19 (Statistical Package for Social Sciences). The quantitative data was represented as mean ± SD, median, and interquartile range (IQR). For comparison, *t* test and analysis of variance were used. The qualitative data was presented as number and percentage. For comparison, X^2 test was used and Fisher's exact test was used instead when the expected frequency is <5. For all tests, a probability value (*P* value) <0.05 was considered statistically significant.

RESULTS

The study included 100 preschool children with recurrent wheezy chest; their age ranged from 2 to 5 years, 68% of them were males, 75% came from rural areas, and other descriptive data of the studied patients are shown in Table 1.

Family history of allergy was found in 66 patients, while history of other allergies was reported in 47 patients. Among these allergies, allergic rhinitis was the most common one (reported in 33 of 47 patients with history of other allergies), viral infection was reported as the most common precipitating factor for wheezing episode, followed by exposure to cold air and dust (reported among 93, 90, and 63 patients, respectively). Among studied patients 55% were born prematurely, and 52% had a history of bronchiolitis (Table 2).

History of food allergy was positive in 47% of the studied patients as reported by their parents, type of the food used to cause allergic symptoms and the clinical presentation are shown in (Table 3).

Out of 53 patients who reported negative allergic symptoms to food, 13 patients had an advice to exclude some kinds of food (especially milk–egg–fish) from diet without actual reaction to the food, especially during the wheezy episode.

SPT was done to all the 100 studied patients and positive results were observed in 28% (for detailed results see Table 4).

Out of the studied patients, 28 patients had positive reaction by SPT. Sensitization to fish was found in 15 patients (11 males and 4 females), sensitization to milk was found in eight patients (six males and two females), sensitization to egg was found in five patients (all were males), and sensitization to wheat was found in four patients (three males and one female); the average diameter of the wheal and flare to the four tested allergens are shown in Table 4. Seventy-five percent of the sensitized patients were males, with fish sensitization being the most prevalent in both males and females.

Eighteen patients out of the 28 patients who were sensitized by SPT gave positive history of food allergy, while ten patients had no suggestive history of food allergy; also, positive history of food allergy was reported in 29 of non-sensitized patients, with a statistically significant *P* value of 0.022.

When comparing the sensitized patients by SPT versus those who were non-sensitized, no statistically significant differences regarding the descriptive data; most of the precipitating factors of the wheezy episodes or the laboratory findings were found (Table 5).

Results showed that history suggestive of food allergy was negative in 35.7% of sensitized patients versus 61.1% of non-sensitized patients ($P = 0.022$).

Early weaning before 4 months by cow's milk protein was significantly higher in the sensitized patients versus those who were non-sensitized (17.9% versus 2.8%, $P = 0.017$) (Table 5).

DISCUSSION

In this study, 100 preschool children aged 2–5 years with recurrent wheezing attending Assuit University Children Hospital were enrolled. Results showed that 68 of them were males. This high prevalence of wheezy chest in males is supported by the study of Abd El-Menem et al.,[11] who found that 63% of the studied Egyptian asthmatic children aged 2–18 years were males, and Turkeli et al.,[12] who showed that 60% of the studied asthmatic preschool children were males.

The reason why prevalence of wheezy chest in females is less than in males may be due to higher size-corrected flow rates and

Table 1. Descriptive, clinical, and lab data of the studied preschool children with recurrent wheezing.

Item	*n* (%) or Mean ± SD
Age (years)	
2–<3	35 (35.0)
3–<4	36 (36.0)
4–≤5	29 (29.0)
Mean ± SD (range)	3.20 ± 0.84 (2–5)
Sex	
Male	68 (68.0)
Female	32 (32.0)
Residence	
Rural	75 (75.0)
Urban	25 (25.0)
Pattern of wheeze	
Episodic	43 (43.0)
Multiple trigger wheeze	47 (47.0)
No. of wheezy episodes in the past year, median (range)	6.0 (3.0–10.0)
No. of hospital admissions in the past year, median (range)	6.0 (3.0–10.0)
Level of asthma control under 5 years	
Controlled	1 (1.0)
Partially controlled	49 (49.0)
Uncontrolled	50 (50.0)
Total leukocytic count ($\times 10^3$ cells/μL)	
Mean ± SD/	9470 ± 4350
Median (range)	8600 (3200–25,800)
Absolute eosinophil count($\times 10^3$ cells/μL)	
Mean ± SD	392.21 ± 465.57
Median (range)	250.0 (0–2190)
Serum IgE level (kIU/L)	
Mean ± SD	476.56 ± 933.26
Median (range)	122.2 (0.8– 5000)

Table 2. Possible underlying and precipitating factors of the wheezy episodes in the studied preschool children with recurrent wheezing.

Item	*n* (%) or mean ± SD
Family history of allergy	
Present	66 (66.0)
Absent	34 (34.0)
Type of allergy in the family	
Asthma	50/66 (75.8)
Eczema	13/66 (19.7)
Allergic rhinitis	12/66 (18.2)
Allergic conjunctivitis	6/66 (9.1)
Food allergy	2/66 (3.0)
Allergic sinusitis	1/66 (1.5)
History of other allergies in the studied patients	
Present	47 (47.0)
Absent	53 (53.0)
Type of other allergies in the studied patients	
Allergic rhinitis	33/47 (70.2)
Eczema	19/47 (40.4)
Allergic conjunctivitis	5/47 (10.6)
Urticaria	3/47 (6.4)
The possible precipitating factors of the wheezy episodes	
Viral infection	93 (93.0)
Cold air	90 (90.0)
Dust	63 (63.0)
Noxious fumes as perfumes	61 (61.0)
Smoke	58 (58.0)
Food allergy	47 (47.0)
Exercise	20 (20.0)
Laughing	15 (15.0)
Presence of animals or birds at home	74 (74.0)
Birds	38/74 (51.4)
Animals	9/74 (12.2)
Both	27/74 (36.5)
History of paternal smoking	
During pregnancy (prenatal)	54 (54.0)
In the presence of the patient (postnatal)	57 (57.0)
Feeding in the first 4 months	
Exclusive breast milk	84 (84.0)
Formula feeding	16 (16.0)
Early <4-month introduction of cow milk protein	7 (7.0)
Early <4-month introduction of cereals and gluten products	4 (4.0)
If the child is born preterm	Yes/no (55/45)
If there is history of bronchiolitis	Yes/no (52/48)

specific airway conductance, probably due to a higher ratio of large to small airways. In addition, there is delayed surfactant production in males, possibly because of androgen production. Enhanced surfactant production in females might lead to increased patency of the small airways, and this could possibly reduce the risk for wheeze later on.[13]

Having a family history of allergy was found in 66% of the studied patients; asthma was the most reported form (75.8% of them). This is in agreement with Elnady et al.,[14] who reported a positive family history in 60% of the studied Egyptian asthmatic children; also, the PASTURE birth cohort study showed that wheezing was positively related to having a family history of allergy.[15] On the other hand, the study by Ball et al.[16] revealed a negative relation between the development of asthma in American children and family history of asthma. The presence of positive family history in many of the wheezy children could be explained by genetic mutations within the immune system that predispose to asthma in the same family.[17]

In our study, viral infections is the most common precipitating factor for the wheezy episodes in this age group, as evidenced by 93% of the parents of the studied patients. The explanation for this finding could be that viral infections are generally recognized as important contributors to acute asthma exacerbations,[18] and that the relationship of infections with asthma is dependent on the timing, type, and/or severity of the infections. It has been suggested that exposure to infections in the first weeks of life may protect against asthma, while respiratory infections contracted after that time may be early signs of asthma, misdiagnosed as asthma, or a cause of asthma.[19]

History suggestive of food allergy was positive in only 64.3% (18/28) of the sensitized patients versus 38.9% (28/72) of the

Table 3. History and the clinical presentation of food allergy in the studied preschool children with recurrent wheezing.

Item ($n = 47$)	n (%)
Food used to cause allergy (by history)	
Fish	32 (68.1)
Egg	26 (55.3)
Milk	19 (40.4)
Banana	17 (36.2)
Strawberry	8 (17.0)
Tomato sauce	4 (8.5)
Chocolate	3 (6.4)
Mango	3 (6.4)
Yoghurt	3 (6.4)
Chicken	1 (2.1)
Wheat	0 (0.0)
Allergic symptoms after food ingestion	
Respiratory	34 (72.3)
Respiratory and cutaneous	13 (27.6)
Time of onset of symptoms after food ingestion	
<1 h	12 (25.5)
1–2 h	30 (63.8)
2–24 h	3 (6.4)
>24 h	2 (4.3)
Recurrence of the symptoms every time the offending food is ingested	
Present	34 (72.3)
Absent	13 (27.7)
Exclusion of the offending food from diet	
Yes	33 (70.2)
No	14 (29.8)

Table 4. Results of the SPT in the studied preschool children with recurrent wheezing.

Type of food with positive reaction ($n = 28$)	n (%) or mean ± SD
Fish	15 (53.6)
Wheal	
Mean ± SD	4.8 ± 1.5
Median (range)	4.5 (3–8)
Flare	
Mean ± SD	11.6 ± 2.9
Median (range)	10 (6–15)
Milk	8 (28.6)
Wheal	
Mean ± SD	6.9 ± 4
Median (range)	5 (4–11.5)
Flare	
Mean ± SD	16.9 ± 10.5
Median (range)	13.5 (9–40)
Egg	5 (17.9)
Wheal	
Mean ± SD	6.2 ± 2.9
Median (range)	5 (4–11)
Flare	
Mean ±SD	17.8 ± 8.4
Median (Range)	15 (10–30)
Wheat	4 (14.3)
Wheal	
Mean ± SD	5.75 ± 50
Median (Range)	6 (5–6)
Flare	
Mean ± SD	12.33 ± 2.52
Median (range)	12 (10–15)

non-sensitized patients ($P = 0.022$). This is augmented by what was previously stated that history is very important as an initial step in the diagnosis of food allergy that will guide further workup as SPT and/or sIgE, but it is better not to depend on only one of them, but both are needed for better screening. SPT appears to have excellent sensitivity and negative predictive power, but poor specificity and positive predictive value in comparison to the gold standard diagnostic oral food challenge test. Some patients with wheal 3–4 mm to specific food, such as for fish, may have no history of reactivity to this food. False-positive fish reactions could be due to relatively high levels of histamine in fish extract.[20]

Also, early weaning before 4 months by cow's milk protein was significantly higher in the group of the patients who were sensitized by SPT versus those who were non-sensitized (17.9% versus 2.8%, $P = 0.017$). This could be explained by early exposure before 4 months to food allergens may be a risk factor for later sensitization by SPT. However, no significant difference was found between the two groups (sensitized patients versus non-sensitized patients) in the other descriptive and clinico-laboratory data.

In our study, 28% of the enrolled patients with recurrent wheezy chest were sensitized to food allergens as indicated by positive SPT to any of the tested food allergen extracts. A wheal of at least 3 mm in diameter or larger is considered positive. In general, the larger the SPT response, the higher the likelihood of clinical relevance. This is consistent with the study by Guilbert et al.[21], as 33% of his studied toddler-aged children with recurrent wheezy chest were sensitized to food allergen extracts.

Non-significant differences between sensitized and non-sensitized children in terms of possible precipitating factors, such as viral infections, dust, smoke (ante- and postnatal), and noxious fumes exposure, could be discussed. Our results show that those are nonspecific triggers and must be avoided regardless of the allergic status.

Among the whole studied patients, the food with the highest prevalence of sensitization by SPT was fish (15 %), followed by milk (8%), egg (5%), and wheat (4%). This is in line with the previous reports in the western countries, showing that nut, milk, soya, egg, seafood, sesame, and wheat are "priority food allergens."[22]

In a previous study conducted on fish sensitization in a group of Egyptian allergic children suffering from various allergic disorders aged 1–15 years old, fish sensitization was observed in 13.8% (12/87) of the allergic patients based on positive SPT. Five of the sensitized patients (5/12) gave a history suggestive of fish allergy compared to two (2/75) of the non-sensitized patients ($P = 0.00$)[23].

In contrast to our observation, the study by Osborne et al.[24] which reported the prevalence rate of allergy to egg white (16.5%) and cow's milk (5.6%) among Australian children, although there was a comparable prevalence rate of cow's milk allergy. Furthermore, in South Africa, the study by Els et al.[25] reported the following prevalence of food allergens: egg white

Table 5. Comparison of the clinico-laboratory characteristics of the studied preschool children with recurrent wheezy chest according to the results of SPT.

Item	Skin prick test (SPT)		*P* value
	Sensitized ($n = 28$)	Non-sensitized ($n = 72$)	
Descriptive data			
Age			
Mean ± SD	3.20 ± 0.98	3.20 ± 0.79	0.778
Sex			
Male	21 (75.0%)	47 (65.3%)	0.349
Female	7 (25.0%)	25 (34.7%)	
Residence			
Rural	18 (64.3%)	57 (79.2%)	0.123
Urban	10 (35.7%)	15 (20.8%)	
Number of wheezy episodes in the past year			
Mean ± SD	5.57 ± 2.79	6.60 ± 2.48	0.05
Median (range)	4.5 (3.0–10.0)	6.0 (3.0–10.0)	
Level of asthma control			
Controlled, *n* (%)	0 (0.0%)	1 (1.4%)	1.000
Partially controlled, *n* (%)	16 (57.1%)	33 (45.8%)	0.310
Uncontrolled, *n* (%)	12 (42.9%)	38 (52.8%)	0.373
Possible underlying and precipitating factors of the wheezy episodes			
Family history of allergy			
Present	18 (64.3%)	48 (66.7%)	0.821
Absent	10 (35.7%)	24 (33.3%)	
Other allergies in the studied patients			
Present	14 (50.0%)	33 (45.8%)	0.708
Absent	14 (50.0%)	39 (54.2%)	
Possible precipitating factors of wheezy episode			
Viral infection	25 (89.3%)	68 (94.4%)	0.396
Cold air	24 (85.7%)	66 (91.7%)	0.460
Dust	17 (60.7%)	46 (63.9%)	0.768
Noxious fumes	15 (53.6%)	46 (63.9%)	0.342
Smoke	14 (50.0%)	44 (61.1%)	0.312
Food allergy	18 (64.3%)	28 (38.9%)	0.022*
Laughing	6 (21.4%)	9 (12.5%)	0.349
Exercise	7 (25.0%)	13 (18.1%)	0.436
Presence of animals and birds at home	18 (64.3%)	56 (77.8%)	0.167
Parental smoking			
During pregnancy	16 (57.1%)	38 (52.8%)	0.694
In the presence of child	15 (53.6%)	42 (58.3%)	0.666
Feeding in first 4 months			
Exclusive breast feeding	23 (82.1%)	61 (84.7%)	0.766
Mixed feeding	5 (17.9%)	11 (15.3%)	
Early <4-month weaning by cow milk protein	5 (17.9%)	2 (2.8%)	0.017*
Early <4-month weaning by cereals and gluten products	3 (10.7%)	1 (1.4%)	0.065
Laboratory findings			
Total leukocytic count ($\times 10^3$ cells/μL)			
Mean ± SD	9.94 ± 5.34	9.29 ± 3.92	0.875
Median (range)	8.1 (4.7–23.0)	9.0 (3.2–25.8)	
Absolute eosnophilic count ($\times 10^3$ cells/μL)			
Mean ± SD	514.32 ± 620.60	344.73 ± 384.20	0.302
Median (range)	294.1 (0.0–2190.0)	231.8 (0.0–1928.5)	
Serum IgE level (kIU/L)			
Mean ± SD	409.66 ± 1020.69	502.57 ± 903.23	0.381
Median (range)	105.7 (0.8–5000.0)	141.6 (3.1–4508.8)	

*Statistically significant ($p < 0.05$.)

(7%), wheat (4%), fish (4%), and milk (3%). This may be attributed to different studied patients or different sample size. Ouahidi et al.[26] stated that the type and prevalence of food allergy vary with geographical location.

In this study, sensitization to fish was the most common type of sensitization observed by SPT among the studied patients with recurrent wheezy chest. Similar to this study, fish sensitization was detected in 4.3% of a group of Swiss infants and children.[27] In addition, fish was the allergen detected on SPT and/or RAST (radioallergosorbent test) in 8% of a case series of children with anaphylaxis from the United Kingodm,[28] and in 30.8% in Ukrainian children with atopic dermatitis.[29] On the contrary, fish sensitization is rare in Swedish children aged 4 years old, this was partly explained by their regular fish consumption before the age of

1 year.[30] Also, a low prevalence of fish sensitization was reported from Germany, where <1% of children up to 17 years of age had a positive SPT.[31]

Prevalence of fish allergy appears to be related to the amount of fish in the local diet. Seafood is a significant sensitizer in up to 40% of Asian children, but allergy on consumption of fish seems lower. Hossny et al.[23] reported that most of the studied Egyptian patients came from economically unprivileged families with poor consumption of fish and other animal proteins; this may explain the higher prevalence of fish sensitization in Egyptian patients.

The majority of patients with positive SPT in this study were males (75%), but this does not reach to be statistically significant gender difference. However, this might be related to the small sample size.[21] This shows that 66.4% of his sensitized studied toddler-aged children were males ($P = 0.03$). However, no gender difference was observed in the prevalence of food sensitization among the Nigerian school-aged children[22], or among Egyptian allergic children.[23]

In our study, no significant differences were found between SPT sensitized and non-sensitized patients regarding total leukocytic count, absolute eosinophilic count, and sIgE levels (Table 5). These results are in line with Naqvi et al.[32] and Wever-Hess et al.,[33] who reported that total IgE and AEC levels were inversely correlated with food allergy and asthma severity.

STUDY LIMITATIONS

- The sample size is relatively small, which decreases the power of the study and does not allow for solid conclusions.
- It can be criticized that the prevalence of food sensitization in wheezy preschool children was probably under-estimated in this study because only four food allergens were tested. This is because of practical and financial considerations. However, the four food allergens that were chosen are the most common at preschool age in our community. Also, the absence of control group can be attributed to financial issues and lack of sufficient kits needed to perform all investigations in another group of control.

CONCLUSION

Food sensitization is common in preschool Egyptian children with recurrent wheezing, with sensitization to fish being the most common type of sensitization observed, followed by milk, eggs, and wheat, respectively. SPT aided by history is a good screening tool to determine whether patients need to avoid some foods that can cause allergy in order to help in controlling their symptoms.

AUTHOR CONTRIBUTIONS

A.M.A., N.S.O., H.A.M., K.A.M., and M.E. carried out history taking and physical examination and SPT of all participants in addition to obtaining blood samples, and participated in the sequence alignment and drafted the manuscript. T.T.H.E. carried out pathological examination of blood. All authors read and approved the final manuscript.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Ethics approval and consent to participate: This study was approved by the ethical committee of Faculty of Medicine, Assiut University, and a written consent was obtained from the participants.

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