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Prevalence of Multiple Foods Sensitization in Pakistani Population

Muhammad Inam,[1] Rubaba Hamid Shafique,[2] Muhammad Irfan,[2] Muhammad Ismail,[3] Shahid Abbas[4] and Nabila Roohi[1]

[1]*Physiology/Endocrinology Lab., Department of Zoology, University of the Punjab, Quaid-i-Azam Campus, Lahore-54590, Pakistan*

[2]*Department of Zoology, University of Arid Agriculture Rawalpindi, Rawalpindi, Pakistan*

[3]*Institute of Biomedical and Genetic Engineering, Islamabad, Pakistan*

[4]*Allergy Asthma and Immunology Centre, Khyber Plaza Fazal-e-Haq Road, Blue Area, Islamabad, Pakistan*

ABSTRACT

Food allergy is an immunological malfunction, categorized as type I hypersensitivity. Many foods share homologous proteins therefore sensitization to one food can result in positive tests or clinical reactivity to related foods developing multiple foods sensitization sometimes leading to the development of allergy symptoms. This study evaluates the prevalence of multiple foods hypersensitivity in Pakistan. Data of allergy patients visiting Allergy Asthma & Immunology Centre, Islamabad was obtained from 2010 to 2013. Standard Skin Prick Test (SPT) was used to detect sensitization to egg, milk, beef, mutton, chicken, fish, peanuts, wheat, rice, soya, corn, banana, pulses and yeast. SPT with house dust mite allergens (Der p1 and Der f1) and mixed pollen allergens from paper mulberry, cocklebur and grasses was also performed. The prevalence of sensitization to food, HDM and pollen allergens was 38%, 80.25% and 53.50% respectively among the sample population. A gender skewness was observed with number of male patients significantly higher ($p<0.0001$) than the female patients. Among the food allergen group tested, the prevalence of wheat, yeast, milk and egg sensitivity was significantly higher ($p<0.0001$). Out of a total of 812 patients where positive SPT was demonstrated, 53% patients showed reaction to 4-6 foods and 29.6% were SPT positive to more than 7 foods. Hence it can be concluded that since atopic individuals are genetically predisposed therefore they are more susceptible to having multiple foods sensitization.

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Authors' Contribution

M Inam and RHS conceived and designed the study, executed experimental work, collected data and wrote the article. M Irfan statistically analyzed the data. M. Ismail and SA provided clinical guidance. NR supervised the work.

Key words

Food sensitization, skin prick test, animal protein sensitization, co-sensitization to allergens.

INTRODUCTION

Allergy is an inappropriate and unusual immune response against exogenous substances (allergens), which are normally harmless (Arshad, 2002). It is categorized as type I hypersensitivity reaction (Roitt *et al*., 1998) mediated by IgE antibodies (Kinet, 1999) leading to symptoms like erythema, urticaria, coughing, wheezing, sneezing, rhinorrhea and more serious conditions such as asthma and anaphylaxis (Beyer and Teuber, 2004). Food allergy is a malfunction of the immune system in response to dietary antigens (Beyer and Teuber, 2004). It refers to the food-triggered immunological mechanisms whether IgE-mediated, non-IgE-mediated, or involving a combination of IgE- and non-IgE-mediated etiologies (WHO, 2003; Boyce *et al*., 2010; Garcia and Lizaso, 2011). All other non-allergic food hypersensitivity reactions may be described as "food intolerance". Food allergy develops when oral tolerance fails to develop normally or break down in genetically predisposed individuals (Sampson, 2003). A number of specific clinical syndromes may occur as a consequence of food allergies (Aalberse *et al*., 2001).

Allergy causing foods contain chemical substances (typically proteins, sometimes with small molecules called haptens) that elicit specific immunologic reactions causing hypersensitivity reactions if eaten uncooked, cooked or sometimes even after they have undergone digestion (Sicherer and Sampson, 2006; Waserman and Watson, 2011; Sampson *et al*., 2014). Out of hundreds of different foods that humans consume, only a small number account for most of the food allergic reactions. In children approximately 90% of hypersensitivity reactions are caused by milk, peanuts, eggs, wheat and soybeans whereas, in adults, fish, shellfish, tree nuts and peanuts account for approximately 85% of allergic reaction (Sicherer and Sampson, 2010; Waserman and Wastson, 2011). Epidemiology studies on food allergy are either based on self-reported allergic reactions or allergy test based prevalence data. Nearly 8% of children and 2% of adults in westernized countries suffer from allergic reactions against various foods (Burbank and Burks, 2015). Around 12 million of Americans are affected by

* Corresponding author: inammuhammad@hotmail.com
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food allergies, including approximately 4% adults, 6% children (<3 years) (Sampson, 2005). Children with atopic disorders tend to have a higher prevalence of food allergy; in Europe, 35% of children with atopic dermatitis have IgE-mediated food allergy (Burks *et al*., 2012) and about 8% of children with asthma have food-induced wheezing (Sampson *et al*., 2004). The National Institute of Allergy and Infectious Disease (NIAID-US) recently concluded that the prevalence of food allergy among all age groups likely falls between 1% and 10% (Boyce *et al*., 2010).

Many foods share homologous proteins; thus IgE-mediated sensitization to one food can result in positive tests or clinical reactivity to related foods (Kattan and Sicherer, 2015; Matsuo *et al*., 2015). Studies have estimated that at least one third of peanut allergic patients are also allergic to at least one tree nut (Sicherer *et al*., 1998). Furthermore, homologous proteins can be shared between foods and pollens, for example, individuals who demonstrate IgE positivity to grass pollens may also be positive for wheat (Sicherer *et al*., 1998), and birch pollen allergic individuals can have positive test results for peanut and hazelnut (Jones *et al*., 1995; Mittag *et al*., 2004; Wang, 2010; Guhsl *et al*., 2015). According to Stanford Alliance for Food Allergy Research (SAFAR) a person with one food sensitization has a 30% chance of developing multiple foods sensitization (Bacal, 2013). Data from published studies provides estimates of multiple foods sensitivity prevalence (Bacal, 2013). A study of food allergies in a highly atopic group of children 57% of children reacted to two or three foods during double-blind, placebo-controlled food challenges (DBPCFC) (Sicherer *et al*., 2008), most of the children giving positive food challenge results also gave a positive skin prick tests (SPTs) to several foods. Egg, peanut, milk, wheat, and soy accounted for about 60% of the positive clinical responses in this study. In the National Cooperative Inner City Asthma Study, more than 500 random serum samples were evaluated for specific IgE to six common food allergens (milk, egg, wheat, soy, peanut, and cod) (Fleischer *et al*., 2011), 27% of children were sensitized to more than one of these foods. More than 95% subjects in this group of children also demonstrated clinical reactivity to at least one of these foods. This group was considered to be a true food allergy group. Within this group, nearly all (96%) had sensitization (>0.35 kU/L) to additional foods, and 25% were sensitized to all six foods tested (Boyce *et al*., 2010).

Pakistan is no exception to this increasing global issue, but no studies are available in literature showing prevalence of sensitivity to various foods consumed as part of diet in Pakistan. The aim of this study was to estimate the prevalence of food sensitization and further evaluate the occurrence of multiple foods sensitivity in patients visiting the Allergy Centre in Islamabad.

MATERIALS AND METHODS

A retrospective study of allergy patients was undertaken at Allergy Asthma & Immunology Centre, Islamabad. The center is visited by patients from the twin cities of Rawalpindi and Islamabad, Khyber Pakhtunkhwa and patients from northern and central Punjab. Data from allergy patients was obtained from 2010 to 2013, according to NIAID USA and WAO guidelines (Boyce *et al*., 2010; Bernstein *et al*., 2008). Medical histories were taken using questionnaires and SPT (also known as a skin puncture test) was performed to assist in the identification of foods that may be causing IgE-mediated food hypersensitivity (Hendrick *et al*., 1975; Fiocchi *et al*., 2010). All new patients between the ages of 7 to 65 years were included in the study. The patients were symptomatic and were suffering from Atopic dermatitis (AD), asthma or other respiratory problems like allergic rhinitis. In our attempt to normalize the data no self-reported, asymptomatic and SPT negative patients were included in this study. Allergen extracts for SPT were purchased from Hollister Stier (Spokane, WA, USA). Food allergens used in the SPT were egg, milk, beef, mutton, chicken, fish, peanuts, wheat, rice, soya, corn, banana, pulses and yeast. In addition to food allergens SPT with house dust mite allergens (Der p1 and Der f 1 mix) and mixed pollen allergen from paper mulberry, cocklebur and grasses were also performed.

SPT test was performed on the volar aspect of the forearms of the subjects. Before the test, they were asked to clean the forearm with soap and water. A drop of all the allergens was placed on the skin and the material was inoculated into the superficial layer of the skin through a gentle prick by lifting the skin with a disposable lancet tip (Bernstein *et al*., 2008). Saline and histamine were also applied as negative and positive controls respectively. At least 3cm distance was kept between the two allergens. After 15 minutes, development of redness and wheal at the site of prick constituted sensitivity. Reaction was considered positive if the diameter of wheal with erythema was >3mm. in the absence of any equivalent reaction in the control test. Patients were not tested if they had any antihistamine drugs within the preceding 48 hours.

Significance was calculated with one-way ANOVA and pairwise comparison was performed with Tukey's multiple comparison test, whereas relative risk was

Table I.- Demographic characteristics of food allergy patients. The Table shows number of patients.

Year	2010 n=260	2011 n=695	2012 n= 701	2013 n=431
Male:	144(55)	376(54)	431(61)	221(51)
Female:	116(45)	319(46)	270(39)	210(49)
Disease presentation (n)				
Food allergy (812)	73(28)	208(30)	329(47)	202(47)
Pollen allergy (1094)	158(61)	417(60)	308(44)	211(49)
HDM allergy (1706)	192(74)	576(83)	602(86)	336(78)

Total patients, 2087; Age: mean ± SD (range), 35 ± 13 (7-65); Age groups (years): <12, 3.12; 12-25.0, 14.88; 25-45, 45.9; 45-60, 31.97; >60, 4.14.

Table II.- Year wise (2010-2013) prevalence of hypersensitivity (ANOVA).

	% prevalence			Food vs HDM				Food vs pollen			
	Food	HDM	Pollen	Difference	95% CI of difference	P value	Summary	Difference	95% CI of difference.	P value	Sum-mary
2010	28	74	61	46.0	-11.36 to 103.4	> 0.05	ns	33.0	-24.36 to 90.36	> 0.05	ns
2011	30	83	60	53.0	-4.359 to 110.4	< 0.05	*	30.0	-27.36 to 87.36	> 0.05	ns
2012	47	86	44	39.0	-18.36 to 96.36	> 0.05	ns	-3.0	-60.36 to 54.36	> 0.05	ns
2013	47	78	49	31.0	-26.36 to 88.36	> 0.05	ns	2.0	-55.36 to 59.36	> 0.05	ns
Mean	38	80.25	53.5	-42.25	-58.63 to -25.87	<0.0001	***	-15.50	-31.88 to 0.88	>0.05	Ns

*, Significant (p value <0.05); ***, highly significant (p value<0.0001); ns, not significant.

calculated with the help of Fisher's exact test. Year-wise data analysis was done to help shed light on possible increasing trends in prevalence of sensitization to various allergen in the population.

RESULTS

The demographic characteristics of patients are summarized in Table I. The occurrence of sensitization to food, HDM and pollen allergens was 38%, 80.25% and 53.50% respectively among the sample population. A year wise prevalence (% positive SPT) of food, HDM and pollen allergy is shown in Figure 1. Tukey's multiple comparison test shows that mean prevalence of HDM sensitization (mean%=80.25) was significantly higher than food ($p<0.0001$) and pollen hypersenstivity ($p<001$), whereas, there was no significant difference observed between the prevalence of food and pollen sensitization. The prevalence of all allergy groups did not change significantly over a period of three years (Table II).

The total number of male patients reporting allergies was significantly higher ($p<0.0001$) than the females. The risk of males having allergies is slightly greater than females (relative risk range between 1.204-1.362 at 95% CI). On the other-hand a greater number of females ($p<0.0001$) were found with positive skin prick test (SPT) to one or more food allergens (Fig. 2). Prevalence of wheat sensitization was highest in the tested food allergens, found in 469 (57.8%) patients visiting the allergy clinic. This was followed by 443 (54.4%) patients showing positive SPT to egg proteins. Sensitization to milk protein was food in 409 (50.4%) patients. More than 50% patients were sensitized to yeast (418 individuals: 51.5%). Meat proteins included in the study were mutton, fish, beef and chicken; 322(39.6%), 322 (39.6%), 325 (40.0%) and 328 (40.4%) patients were SPT positive to these allergens, respectively. Corn,

lentils, peanuts, rice and soya are the remaining food allergens tested here. Sensitization to these food allergens was observed in 327 (40.4%), 322 (39.6%), 238 (29.3%), 256 (31.5%) and 253 (31.1%) patients, respectively. A small group of patients 147 (18.1%) was found to be sensitized against banana (Table III).

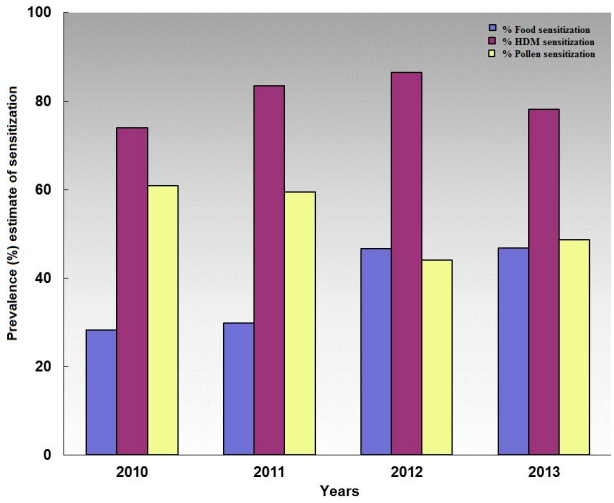

Fig. 1. Prevalence (%) estimates of allergen sensitization from 2010-2013.

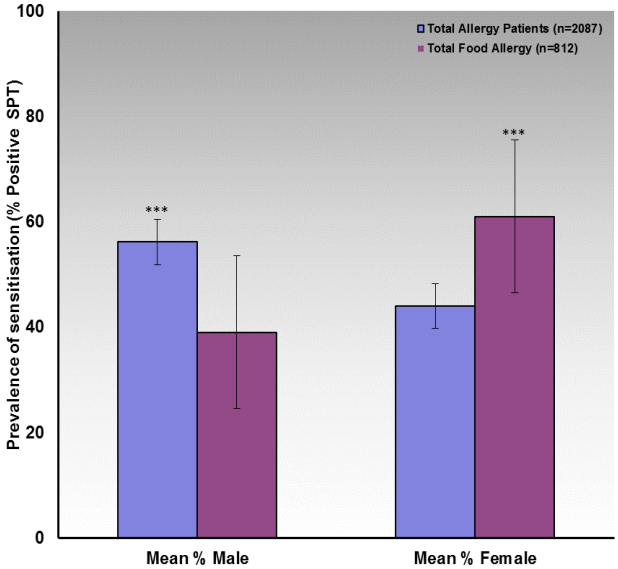

Fig. 2. Percentage of total allergies and food allergies in Genders (***: highly significant).

Out of the 812 food allergy patients, only 1.1% were sensitized to just one food. At least 53% showed reaction to 4-6 foods and 29.6% were positive to greater than 7 foods (Table IV).

Table III.- Sensitization of patients to food allergens.

Allergens		Number (n=812)	Percentage (%)
Animal source proteins	Mutton	322	39.6
	Fish	322	39.6
	Milk	409	50.4
	Beef	325	40.0
	Chicken	328	40.4
	Egg	443	54.4
Plant source foods	Peanut	238	29.3
	Rice	256	31.5
	Soya	253	31.1
	Corn	327	40.4
	Wheat	469	57.8
	Banana	147	18.1
	Lentils	322	39.6
Others	Yeast	418	51.5

Table IV.- Sensitization of patients to multiple food allergens.

Number of food types	Patients	
	Positive SPT (n=812)	%age
1	9	1.1
2	48	5.9
3	84	10.4
4	141	17.4
5	186	23.0
6	103	12.6
7	106	13.0
8	54	6.7
9	30	3.7
10	3	0.4
11	3	0.4
12	3	0.4
13	3	0.4
14	39	4.8
< 4	141	17.4
4-6	430	53.0
> 7	241	29.6

DISCUSSION

The prevalence of food allergy is increasing globally (Waserman and Watson, 2011). The Centers for Disease Control and Prevention (CDC) report that the number of children with food allergies grew by 50 percent between 1997 and 2011 (Jackson *et al*., 2013). Despite being among the most common chronic non-communicable diseases quality data on the burden of

these illnesses is lacking, especially among the developing countries. Researchers have emphasized a need to increase the knowledge about prevalence and pathophysiology of food allergy for the development of improved methods for prevention, diagnosis, and management of the disorder (Chafen *et al*., 2010; Waserman and Watson, 2011). Earlier reports show inconsistency in the prevalence of food hypersensitivity, varying from 3.24% to 34.9% (Boyce *et al*., 2010). There are limited reports on the prevalence rates of sensitization to food allergens in low economy countries of the world. Pakistan is also in the list of those countries where food sensitivity has been ignored at scientific or governmental level. Here we report that 39% of symptomatic allergy patients were sensitized to one or more food allergens, this is in accordance to a recent study by Centers for Disease Control and Prevention (CDC) (Jackson *et al*., 2013). In a previous study from Pakistan 2.3% food allergy was reported among the allergy patients (Ali *et al*., 2005). This contradiction can be explained partly by the difference in methodology used in a given study (Boyce *et al*., 2010). Year wise analysis of our data did not show any significant change in the prevalence rate of food sensitization (based on SPT) over the past few years contradicting earlier reports of increasing trends in food sensitivity (Simpson *et al*., 2008; Akinbami *et al*., 2015). In overall allergy patients the number of male patients were significantly higher ($p<0.0001$) than the female patients, while occurrence of sensitivity reactions to food allergens was higher ($p<0.0001$) in female patients. Few studies have investigated the gender bias in risk to various food allergens, however a report from Norway shows that 61% females gave allergic reactions to food over 40% male (Dunngalvin *et al.*, 2006). In the present work we found that sensitization to wheat, egg and milk allergens was the most prevalent in the allergy patients. Researchers from other parts of the world have reported similar data (Branum and Lukacs, 2009). High level of egg allergy has previously been reported in Europe (Boyano-Martinez *et al*., 2002) and United States (Sicherer *et al*., 2014). Through this research we observed that 53% patients showed reaction to 4-6 foods and 29.6% were SPT positive to more than 7 foods, results are comparable to previous reports of multiple sensitization (Gupta *et al*., 2004; Fiocchi *et al*., 2015). Our findings are coherent with earlier reports which say that atopic patients are at greater risk of showing sensitization to multiple foods (Burks *et al*., 1998; Just *et al*., 2014; Welch and Sampson, 2015).

CONCLUSION

Here, we conclude that, atopic individuals are more susceptible to having multiple foods sensitization. This study is an attempt to evaluate the gravity of food hypersensitivity in Pakistan and to better anticipate and address this rising community and health service burden. Further research is required to estimate a correlation between SPT based sensitization and development of symptomatic food allergy.

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Statement of conflict of interest

Authors have declared no conflict of interest.

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