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DOES SKIN PRICK TEST POSITIVITY TOWARD RESPIRATORY AND FOOD ALLERGENS DIFFER IN CHILDREN WHEN COMPARED TO ADULTS IN THE SAME GEOGRAPHIC AREA

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ABSTRACT

Abstract: The research was undertaken to compare the probable allergens through skin prick test (SPT) in allergic children and adults in the same geographic area. In symptomatic individuals SPT positivity toward 18 aero and food allergens were assessed and analyzed. Children were more SPT positive but when each allergen was compared between the two group, despite minor variations no significant difference was observed.

Objectives: The aim of this study was to evaluate the profile of skin prick test reactivity to a battery of 18 allergens in symptomatic children and adults in the same geographic area. By comparing results in this two group we tried to make deductions regarding gene- environment interaction.

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INTRODUCTION

This cross-sectional study analyzed the results of skin prick tests (Bousquet *et al* 2012) in allergic individuals. For each allergen, researchers compared results between adults and children.

Allergy is a systemic immune disease but manifestations are seen at the interface of organs with the environment, namely the skin, the respiratory tract, and the gastrointestinal tract. Multiple genetic factors are agents in allergic response. Allergic diseases have a genetic background thus takes its origin very early in life (Lockett GA *et al*, 2015). Interaction between susceptible genes and environment results in clinical disease. Multiple genes each with a modest effect combine with environmental influences and result in clinical phenotype of the disease. It has long been recognized that allergic diseases run in families F0-F1-F2. (Gerrard *et al*, 1976). Twin studies both monozygotiz (100 percent DNA similarity) and dizygotiz (50 percent DNA similarity) are another proof of genetics of allergic disease. (Hemminki *et al*, 2007, Hopp R. *et al*, 1984).

Epidemiologic studies also supports the genetic factors. Genetic factors determine susceptibility also early environment especially microbiota within the gastrointestinal tract effect the immune system and developing organ systems. (Lockett GA, *et al*, 2015. Lynch SV *et al*, 2016) Mucosal tolerance is also initiated at this interfaces so mucosal surfaces have central role in building of mucosal and systemic immunity and susceptibility to non communicable chronic inflammatory

disease and immune disease. Genetic basis of allergy can be explained in 5 steps.1-genes regulate response to environmental allergens and adjust detoxifying enzyme activity against oxidative stress such as tobacco smoke and pollution2-there are genes involved in maintaining integrity of the epithelial barrier at the mucosal surface.3-Genes also regulate Th1/Th2 differentiation and response.Th2 response is primarily involved in immediate allergic processes.4-Genes are involved in determining the tissue response to chronic inflammation and production of profibrotic cytokine TGF_BETA 5-There are disease modifying genes that modify frequency and severity of disease and also response to therapy (Holloway CV. *et al*, 2010).

The study included 125 adults and 44 children patients with various allergic symptoms and diseases. No symptom is pathognomonic so, allergy related diseases are evaluated by clinical examination and questionnaires. These patients were referred for skin prick test toward aero and food allergens. Urticaria, allergic rhinocconjunctivitis, asthma, atopic eczema food intolerance cases from the specialties of ENT, respirology, paediatrics and dermatology were evaluated toward dust mites, grass, tree, mushroom, cockroach, ragweed and eleven food allergens with skin prick test. Chronic allergic skin disorders are the inflammatory and proliferative conditions in which both genetic and environmental factors play important roles.Chronic idiopathic urticaria and atopic dermatitis are among the most common allergic skin disorders. These can be produced by various food and aeroallergens. Skin prick test represents a cheap, easy to perform, simple and highly sensitive

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method to diagnose type I hypersensitivity. The main limitation of the skin test is that a positive reaction does not necessarily mean the patient will experience symptoms. Positive skin tests with a history suggestive of clinical sensitivity strongly incriminate the allergen as a contributor to the disease process. For food allergy in children it has been proposed that a strong positivity toward an allergen may negate an oral food challenge test (Bains *et al*, 2015). Skin prick test is able to detect the presence of allergen specific immunoglobulin E antibodies although they have low specificity. For instance for cow's milk, negative predictive accuracies are between 20 and 86 percent. (Ro AD. *et al*, 2014) We also know that immunoglobulin E mediated food allergy affects 6-8 percent of children. Most patients achieve tolerance to milk by the age of five years. (Mazigh S. *et al*, 2015). For food allergy gold standard is oral food challenges however they are resource consuming and potentially dangerous. But positive skin test or serum IgE test may not have clinical implications because some patients can eat the related food without difficulty. Regarding the diagnostic accuracy of SPT even if it is combined with IgE test, positive predictive value is not absolute. The advantage of skin testing is that it uses an end organ response, is less expensive, is more sensitive and provides immediate results which are easily visualised by the patient. (Peters RL. *et al*, 2012)

Among children with atopic dermatitis the positive predictive accuracies of skin prick tests vary between 69 and 100 percent. (Yang Z. *Et al*, 2015).

On the other hand to diagnose sensitization toward house dust SPT is the gold standard. (Wang YL. *et al*, 2006).

Cockroach sensitization is an important risk factor for the development of asthma. Genetic factors may also play an important role in conferring the susceptibility to cockroach sensitization. Researchers are under way to illuminate genetic basis for cockroach sensitization and development of asthma. (Do DC. *et al*, 2015).

A commonly used method in skin prick tests is to measure average diameter of wheal. A more accurate method is to scan the area of the wheal to calculate the actual size and is recommended in academic research. However in clinical practice the average diameter method is also useful and more practical. Wheal size is critical because small changes correspond to big differences in sensitivity. (Dreborg S. *et al*, 1989).

Researcher's main reason in comparing the results of SPT in children and adults was to draw attention to the genetics of allergic diseases. If environment was more effective we would see an increasing allergy into adulthood. As data gathers with this kind of studies that will give impetus to further genetic researches.

Findings

This study was conducted on 124 adults and 44 children between and Patients with allergic symptoms or allergic diseases between 3 and 67 years old were enrolled in this study consecutively. Distribution of gender and symptoms are shown

in table 1. Respiratory and food allergens tested in skin prick tests and the results are shown in table 2.

Table 1 Distribution of symptoms and demographic characteristics

		Min-Max	Mean±Sd
Age (year)		3-67	31,25±16,26
		n	%
Gender	Male	58	34,5
	Female	110	65,5
Symptom	Urticaria	154	36,9
	Sneezing	4	6,5
	Sneezing, nasal congestion	1	1,6
	Sneezing, postnasal discharge	1	1,6
	Asthma	2	3,2
	Pharyngeal irritation	1	1,6
	Postnasal discharge, cough	1	1,6
	Wheezing	1	1,6
	Cough	2	3,2
	Urticaria, nasal congestion	1	1,6

Table 2 Distribution of Allergens

	0	1+	2+	3+	4+
	n (%)	n (%)	n (%)	n (%)	n (%)
House dust D. P	27 (16,1)	73 (43,5)	45 (26,8)	17 (10,1)	6 (3,6)
House dust D. F	40 (23,8)	77 (45,8)	42 (25,0)	8 (4,8)	1 (0,6)
Grass C1	63 (37,5)	81 (48,2)	20 (11,9)	4 (2,4)	-
Tree (d1-A2)	75 (44,6)	78 (46,4)	14 (8,3)	1 (0,6)	-
Mushroom B2	90 (53,6)	59 (35,1)	17 (10,1)	2 (1,2)	-
Ragweed D2	111 (66,1)	45 (26,8)	11 (6,5)	1 (0,6)	-
Cockroach	155 (92,3)	10 (6,0)	3 (1,8)	-	-
Cow's milk	141 (83,9)	26 (15,5)	1 (0,6)	-	-
Boiled egg	138 (82,1)	29 (17,3)	1 (0,6)	-	-
Chicken	140 (83,3)	24 (14,3)	4 (2,4)	-	-
Cacao	144 (85,7)	24 (14,3)	-	-	-
Tomatoe	160 (95,2)	7 (4,2)	1 (0,6)	-	-
Strawberry	154 (91,7)	14 (8,3)	-	-	-
Bovine meat	162 (96,4)	6 (3,6)	-	-	-
Blackpepper	137 (81,5)	30 (17,9)	1 (0,6)	-	-
Egg white	168 (100,0)	-	-	-	-
Egg yolk	168 (100,0)	-	-	-	-
Fish	159 (94,6)	9 (5,4)	-	-	-

Positive sensitivity scores toward house dust d.p and house dust d.f were similar, and did not show a statistically significant difference.

Grass allergy incidence was higher in in children, but this result also was not statistically significant.

Tree pollen allergy was more prevalent in adults but the difference was not significant.

We could not find any significant difference between adults and children regarding ragweed, cow's milk, boiled egg, egg yellow and fish allergen reactivity scores.

Allergy toward cockroach was more prevalent in adult patients. This reactivity was statistically significant when compared to the children. (p=0,026;p<0,05)

Allergy toward cacao was lower in adults but there was no statistically significant difference between the two groups.

Table 3 Distribution of allergen positivity in groups

		ADULTS	CHILDREN(44)	p				
		(n=124)	n (%)					
House dust D. P	Negative	15 (12,1)	12 (27,3)	0,213	Bovine meat	Negative	122 (98,4)	
	1+	56 (45,2)	17 (38,6)			1+ 2 (1,6)	4 (9,1)	
	2+	39 (31,5)	6 (13,6)			Md±Sd	0,02±0,13	0,09±0,29
	3+	9 (7,3)	8 (18,2)			Median	0,0	0,0
	4+	5 (4,0)	1 (2,3)			Negative	105 (84,7)	32 (72,7)
	Md±Sd	1,46±0,94	1,30±1,13			1+ 19 (15,3)	11 (25,0)	
House dust D. F	Median	1,0	1,0	0,431	Blackpepper	2+ 0 (0,0)	1 (2,3)	
	Negative	27 (21,8)	13 (29,5)			Md±Sd	0,15±0,36	0,30±0,51
	1+	59 (47,6)	18 (40,9)			Median	0,0	0,0
	2+	30 (24,2)	12 (27,3)			Negative	124 (100,0)	44 (100,0)
	3+	7 (5,6)	1 (2,3)			Md±Sd	0,00±0,00	0,00±0,00
	4+	1 (0,8)	0 (0,0)			Median	0,0	0,0
Grass C1	Md±Sd	1,16±0,86	1,02±0,82	0,098	Egg white	Negative	124 (100,0)	
	Median	1,0	1,0			Md±Sd	0,00±0,00	0,00±0,00
	Negative	43 (34,7)	20 (45,5)			Median	0,0	0,0
	1+	60 (48,4)	21 (47,7)			Negative	124 (100,0)	44 (100,0)
	2+	18 (14,5)	2 (4,5)			Sd±Sd	0,00±0,00	0,00±0,00
	3+	3 (2,4)	1 (2,3)			Median	0,0	0,0
Tree (d1-A2)	Md±Sd	0,85±0,75	0,64±0,68	0,013*	Egg yolk	Negative	119 (96,0)	
	Median	1,0	1,0			1+ 5 (4,0)	4 (9,1)	
	Negative	49 (39,5)	26 (59,1)			Md±Sd	0,04±0,20	0,09±0,29
	1+	61 (49,2)	17 (38,6)			Median	0,0	0,0
	2+	13 (10,5)	1 (2,3)			Negative	124 (100,0)	44 (100,0)
	3+	1 (0,8)	0 (0,0)			1+ 5 (4,0)	4 (9,1)	
Mushroom B2	Md±Sd	0,73±0,68	0,43±0,54	0,071	Fish	Md±Sd	0,04±0,20	
	Median	1,0	0,0			Median	0,0	0,0
	Negative	62 (50,0)	28 (63,6)			Negative	124 (100,0)	44 (100,0)
	1+	45 (36,3)	14 (31,8)			Sd±Sd	0,00±0,00	0,00±0,00
	2+	15 (12,1)	2 (4,5)			Median	0,0	0,0
	3+	2 (1,6)	0 (0,0)			Negative	119 (96,0)	40 (90,9)
Ragweed D2	Md±Sd	0,65±0,75	0,41±0,58	0,176	Mann-whitney U test	1+ 5 (4,0)	4 (9,1)	
	Median	0,5	0,0			Md±Sd	0,04±0,20	0,09±0,29
	Negative	78 (62,9)	33 (75,0)			Median	0,0	0,0
	1+	37 (29,8)	8 (18,2)			Negative	124 (100,0)	44 (100,0)
	2+	8 (6,5)	3 (6,8)			Sd±Sd	0,00±0,00	0,00±0,00
	3+	1 (0,8)	0 (0,0)			Median	0,0	0,0
Cockroach	Md±Sd	0,45±0,65	0,32±0,60	0,026*	For bovine allergy there was a statistically significant difference between the two groups. Allergen positivity was significantly lower in adults. (p=0,063;p>0,05)	Negative	124 (100,0)	
	Median	0,0	0,0			1+ 5 (4,0)	4 (9,1)	
	Negative	111 (89,5)	44 (100,0)			Md±Sd	0,04±0,20	0,09±0,29
	1+	10 (8,1)	0 (0,0)			Median	0,0	0,0
	2+	3 (2,4)	0 (0,0)			Negative	124 (100,0)	44 (100,0)
	Md±Sd	0,13±0,40	0,00±0,00			Sd±Sd	0,00±0,00	0,00±0,00
Cow's milk	Median	0,0	0,0	0,149	Also allergy toward black pepper was lower in adults but results did not show a statistically significant difference.	Negative	124 (100,0)	
	Negative	107 (86,3)	34 (77,3)			1+ 5 (4,0)	4 (9,1)	
	1+	17 (13,7)	9 (20,5)			Md±Sd	0,04±0,20	0,09±0,29
	2+	0 (0,0)	1 (2,3)			Median	0,0	0,0
	Md±Sd	0,14±0,34	0,25±0,49			Negative	124 (100,0)	44 (100,0)
	Median	0,0	0,0			Sd±Sd	0,00±0,00	0,00±0,00
Boiled egg	Negative	105 (84,7)	33 (75,0)	0,160	While the number of symptomatic patients was higher in SPT positive adults, overall children were more asymptomatic. The number of symptomatic adults was significantly higher than children. (p=0,037; p<0.05) (Table 4)	Negative	124 (100,0)	
	1+	18 (14,5)	11 (25,0)			1+ 5 (4,0)	4 (9,1)	
	2+	1 (0,8)	0 (0,0)			Md±Sd	0,04±0,20	0,09±0,29
	Md±Sd	0,16±0,39	0,25±0,44			Median	0,0	0,0
	Median	0,0	0,0			Negative	124 (100,0)	44 (100,0)
	Negative	104 (83,9)	36 (81,8)			Sd±Sd	0,00±0,00	0,00±0,00
Chicken	1+	18 (14,5)	6 (13,6)	0,704	Statistical Analysis	Negative	124 (100,0)	
	2+	2 (1,6)	2 (4,5)			1+ 5 (4,0)	4 (9,1)	
	Md±Sd	0,18±0,42	0,23±0,52			Md±Sd	0,04±0,20	0,09±0,29
	Median	0,0	0,0			Median	0,0	0,0
	Negative	110 (88,7)	34 (77,3)			Negative	124 (100,0)	44 (100,0)
	1+	14 (11,3)	10 (22,7)			Sd±Sd	0,00±0,00	0,00±0,00
Cacao	Ort±SS	0,11±0,32	0,23±0,42	0,063	We used NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah USA) to analyze test results. Besides statistical methods (mean, standart deviation median, ratio) to compare small groups not showing normal distribution Mann Whitney U test was used .To compare qualitative data Yates Continuity Correction Test was used.(Yates corrected Ki-kare) P<0.01 and p<0.05 levels were considered to be significant.	Negative	124 (100,0)	
	Median	0,0	0,0			1+ 5 (4,0)	4 (9,1)	
	Negative	120 (96,8)	40 (90,9)			Md±Sd	0,04±0,20	0,09±0,29
	1+	4 (3,2)	3 (6,8)			Median	0,0	0,0
	2+	0 (0,0)	1 (2,3)			Negative	124 (100,0)	44 (100,0)
	Md±Sd	0,03±0,18	0,12±0,39			Sd±Sd	0,00±0,00	0,00±0,00
Tomato	Median	0,0	0,0	0,113	Ultimate presentation of allergic diseases is build on a genetic predispositon with later environmental exposure. (Custovic A. 2015). Genetics of allergy is an active research area. Both skin and mucosal barrier defects exposing environmental particles upon an immune abnormality seem to initiate march toward atopy (Soyka MB. Et al, 2012, Matter K. Et al, 2014, De Benedetto. et al, 2011).	Negative	124 (100,0)	
	Negative	115 (92,7)	39 (88,6)			1+ 5 (4,0)	4 (9,1)	
	1+	9 (7,3)	5 (11,4)			Md±Sd	0,04±0,20	0,09±0,29
	2+	0 (0,0)	1 (2,3)			Median	0,0	0,0
	Md±Sd	0,07±0,26	0,11±0,32			Negative	124 (100,0)	44 (100,0)
	Median	0,0	0,0			Sd±Sd	0,00±0,00	0,00±0,00
Srawberry	Negative	115 (92,7)	39 (88,6)	0,399	Mutations in genes result loss of function of a skin barrier protein filaggrin (Irvine AD. et al, 2011). A second barrier defect is shown in tight junction proteins, claudin-1 and claudin-23 in atopic dermatitis patients (De Benedetto. et al, 2011). Loss of integrity of skin barrier allows increased entry of allergens and increased transepidermal loss of water resulting in skin inflammatory response.	Negative	124 (100,0)	
	1+	9 (7,3)	5 (11,4)			1+ 5 (4,0)	4 (9,1)	
	2+	0 (0,0)	1 (2,3)			Md±Sd	0,04±0,20	0,09±0,29
	Md±Sd	0,07±0,26	0,11±0,32			Median	0,0	0,0
	Median	0,0	0,0			Negative	124 (100,0)	44 (100,0)
	Negative	120 (96,8)	40 (90,9)			Sd±Sd	0,00±0,00	0,00±0,00

associated with a drug or food allergy or with infection. Chronic urticaria which is a continuous disease exceeding 6 weeks occurs in 1 percent of the population at any time. In most cases it is difficult to identify a cause, but up to 1/3 of these patients have autoimmune urticaria. Other subgroups are dermographic, delayed pressure, cholinergic, cold contact, heat contact, exercise induced, aquagenic, cold and vibratory urticaria. Histopathologic examination shows degranulated mast cells in the dermis. (Schmitz Zuberbier T. *et al*, 2014).

More recent studies point to important gene-environment interactions in the development of food sensitization. (Dreskin SC 2006). There is a strong genetic contribution to peanut allergy. Monozygotic twins have 64 % concordance for peanut allergy; dizygotic twins have 7% concordance. (Sicherer SH. *et al*, 2014). Variations in gene polymorphism were proposed for food and peanut allergy. (Sampson HA. *et al*, 2014). Food allergy primarily effect children. Main reasons are deficiency of secretory IgA and IgM, insufficient production of gastric acid, immature villous system of intestines, insufficiency of proteolytic enzymes and nonsatisfactory immuntolerance provided by the immune system. (Sicherer SH. *et al*, 2014) Many of these patients outgrow their allergy by the age of 5 years.

Typical signs and symptoms of allergic rhinitis with or without conjunctivitis include some combination of congestion, sneezing, rhinorrhea (anterior and/or posterior), and pruritus of the nose, eyes, oral mucosa, or face and watering and redness of the eyes. Nasal congestion frequently alternates between both sides of the nose as a function of the physiologic nasal cycle. Nasal congestion frequently alternates between both sides of the nose as a function of the physiologic nasal cycle. In addition, during sleep, the dependent side of the nose may become preferentially obstructed. Persistent unilateral obstruction strongly suggests the possibility of an anatomic defect (e.g., nasal septal deviation, concha bullosa of the middle turbinate), inflammatory mass (e.g., nasal polyp), or tumor. Sneezing may be extremely variable but in allergic disease often marked by explosive paroxysms of 5 to 10 sneezes or more. In allergic rhinitis, rhinorrhea most often is clear to white in color, and the presence of purulent secretions strongly indicates the possibility of chronic sinusitis or atrophic rhinitis. Ocular signs and symptoms, including redness, itching, and watering, constitute a major cause of suffering in at least half of the patients with allergic rhinitis (Eccles R 1996). Allergy skin testing using the prick-puncture method is considered to provide the best combination of sensitivity and specificity, although in-vitro testing has demonstrated comparable performance characteristics for some but not all allergens. Allergic rhinitis and asthma show a close association (Laynaert B. *et al*, 2004). The available data regarding the epidemiology of chronic rhinitis in adults are much more limited. Based on data for 15 394 adults of 20 to 44 years of age, in the European Community Respiratory Health Survey I (ECRHSI), the prevalence of allergic rhinitis ranged from 4.6% in Oviedo, Spain, to 31.8% in Melbourne, Australia)In the most recent (US) National Health and Nutrition Examination Survey (NHANES), conducted in 2005–2006, the 12-month prevalence of rhinitis for the entire cohort was 23.5 %, with a

peak of 31.3% in patients 40 to 49 years of age. (Salo PM. *et al*, 2011).

Asthma usually begins in early childhood, although it may later remit (sometimes recurring in adult life). Of asthma sufferers, 95% have their first episode of wheezing before the age of 6 years. (Martinez FD. *et al*, 1995). A US study found the incidence of asthma in the first year of life as 3%, dropping to 0.9% and then to 0.1% in the age group 1 to 4 years and after the age of 15 years, respectively. Adult onset asthma is unusual, with an estimated incidence of 4.6 cases per 1000 person-years in females and 3.6 in males. (de Nijs SB1. *et al*, 2013). Increasing numbers of genes have been identified as asthma-susceptibility genes by the use of genome wide association studies (Koppelman GH. *Et al* 2002, Paternoster L. *et al*, 2012, Castro-Giner F. *et al*, 2009).

CONCLUSION

The overall rate of sensitization to any allergen was.....percent with a cut off (SPT>3 mm) in symptomatic allergic individuals.

If environmental factors were operational in allergies we would see allergic sensitization with a higher percentage in adults. But there seems no increased positivity in adults toward allergens. For instance cow's milk allergy diminishes when children reach five years of age. Atopic dermatitis and asthma in 90 percent of cases present before five years of age.

In the literature we see few skin prick test studies comparing adults and children in the same geographic location. If environmental factors were more effective than genetic susceptibility we would see a rising incidence in allergen sensitivity in adults in this study. Our observations and the results of this study do not support this thought.

This study does not have an asymptomatic control group because of ethical considerations but enrollment of patients consecutively reduces bias.

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