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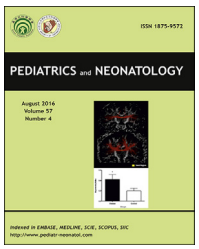

Original Article

Association of body mass index and season with histamine skin reactivity in Chinese children with allergic rhinitis

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Key Words
Allergic rhinitis;
Body mass index;
Children;
Histamine;
Skin prick test

Abstract *Background:* To investigate the association between histamine skin reactivity and body mass index (BMI) and other clinical factors, 526 children (3–6 years old) who underwent a skin-prick test (SPT) to diagnose allergic rhinitis were enrolled.
Methods: The SPT was carried out using 43 common allergens (commercial kit). The wheal size was analyzed. The associations between histamine reactivity and age, gender, BMI, atopy, parental smoking history, and testing season were examined.
Results: Mean age was 4.6 ± 1.1 years. Among all 526 children, 202 (38.4%) had intermittent allergic rhinitis (IAR), 164 (32.1%) had IAR + persistent allergic rhinitis (PER), and 160 (30.4%) had PER. The size of the histamine skin wheal and maximum diameter for positive allergens showed significant seasonal differences ($P = 0.001$ and $P = 0.02$, respectively). Children with biparental allergy history had a higher BMI ($P = 0.006$). BMI ($P < 0.001$), summer testing ($P = 0.001$), and autumn testing ($P < 0.001$) were independently associated with the size of the histamine skin wheal. Only winter testing was independently associated with the maximal diameter for positive allergens ($P = 0.002$).
Conclusions: Higher histamine skin reactivity was associated with higher BMI and summer or autumn testing. Subject BMI and season should be considered for better interpretation of the SPT. The mechanisms underlying these associations require further study.
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1. Introduction

Among Chinese children, 3.1−9.8% suffer from asthma, allergic rhinitis, and/or eczema.[1] Although most cases of allergic diseases are not life-threatening, their prevalence is increasing and they contribute to impair the activities of daily life such as work, sleep, social interactions, and study.[2] In addition, allergic diseases impose an important socioeconomic burden on the patients.[3] Various tests are available for the diagnosis of allergic diseases, including the provocation test, skin prick test (SPT), and multiple allergen simultaneous test. Each of these tests has advantages and limitations, and the SPT is commonly used.[4]

During the SPT, histamine is used as a positive control to rule out false-negative results and as a comparator for the allergic reactions. Nevertheless, histamine skin reactions may be affected by drugs, disease history, method of testing, age, gender, testing season, examiner, and pricking device, resulting in wide variations of the histamine skin reactions among individuals.[4−8] There is still a lack of understanding about differences among individuals regarding the skin reactivity to histamine.

Obesity may be associated with allergic diseases (including atopy, asthma, and allergic rhinitis) in children.[9−11] Furthermore, body mass index (BMI) may be associated with bronchial hyper-responsiveness.[9,12] Nevertheless, the relationship between histamine skin reactivity and BMI is poorly understood.

Therefore, the aim of the present study was to investigate the association between histamine skin reactivity and BMI and other clinical factors. The results of the present study could help in the standardization of the SPT.

2. Methods

2.1. Study design and patients

This was a cross-sectional study of children referred to the Departments of Otolaryngology of the Beijing Edencare Hospital and Beijing Unicare Hospital between January 2015 and December 2015. The inclusion criteria were: 1) showing allergic nasal symptoms such as nasal obstruction, watery rhinorrhea, sneezing, and itching of the nose; 2) being 3−6 years of age; and 3) having undergone a SPT. The exclusion criteria were; 1) use of oral or nasal corticosteroids and antihistamines within 7 days before the SPT; 2) use of any allergy or cold medication within 7 days before the SPT; 3) chronic immune-related diseases such as chronic renal failure or cancer; 4) eczema or dermographism; and 5) histamine skin wheal <3 mm during the SPT. Finally, 526 subjects were included in the present study.

This study was approved by the medical ethics committee of the hospital. All patients gave written informed consent for inclusion.

2.2. SPT

At our center, 21 groups (43 allergens) of commercial standardized allergens (Allergopharma GmbH & Co. KG, Reinbek, Germany) are used for the SPT. The allergens include: dust mites (Dermatophagoides farina and Dermatophagoides pteronyssinus), insects (Blattella germanica), trees (birch, Fagus, Quercus, Platanus, Corylus L., Populus, elm family, Salix, Alnus cremastogyne), Chenopodium album, Humulus, dandelion, English plantain, giant ragweed, black locust, Candida albicans, pine, animals (cat, dog, rabbit, hamster, and guinea pig), gramineous plants/cereals (barley, oats, rye, wheat, swan grass, Dactylis glomerata, ryegrass, timothy, alpine rush, and shelter grass), Aspergillus fumigatus, Penicillium notatum, Curvularia lunata, and Alternaria tenuis.

Histamine hydrochloride (1 mg/mL; Allergopharma GmbH & Co. KG, Reinbek, Germany) was used as the positive control. The negative control was saline 0.9% containing 50% glycerin. A 23G lancet was used for the SPT on the forearms. The size of each wheal was calculated after 15 min as the mean of the longest diameter and the diameter perpendicular to the longest diameter at the midpoint. A wheal ≥ 3 mm was considered positive. The number of positive reactions was used to determine the category of allergic sensitization: none, mono-, or polysensitization.

2.3. Other variables

Gender, height, weight, BMI (kg/m^2), parental smoking status (self-reported), and allergy history (self-reported) were determined. Parental smoking status was classified as smokers (at least one parent) or non-smokers. Parental allergic history was self-reported and included asthma, allergic rhinitis, and atopic dermatitis; the allergy history was categorized by the number of parents with allergic diseases. Intermittent allergic rhinitis (IAR) or persistent allergic rhinitis (PER) was classified based on the definitions provided in the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 guidelines.[13]

2.4. Statistical analysis

Continuous data are presented as the mean ± standard deviation and were analyzed using Student's t-test or ANOVA with Tukey's post-hoc test, as appropriate. Multivariate regression was performed to confirm the independent effects of factors on histamine reactivity. Age, gender, BMI, allergic sensitization, parental smoking, and testing season were included in the analysis. All statistical analyses were conducted with SPSS (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the patients

The baseline data of the 526 children (3−6 years old) with allergic rhinitis are shown in Table 1. Mean age was 4.6 ± 1.1 years. Among all 526 children, 202 (38.4%) had IAR, 164 (32.1%) had IAR + PER, and 160 (30.4%) had PER.

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Table 1 Characteristics of the patients.

Variables	N = 526
Age (years)	4.6 ± 1.1
Type of allergic rhinitis	
IAR	202 (38.4%)
PER	164 (31.2%)
IAR + PER	160 (30.4%)
Gender	
Male	279 (53%)
Female	247 (47%)
Body mass index (kg/m^2)	15.7 ± 1.3
Season	
Spring	136 (25.9%)
Summer	113 (21.5%)
Autumn	176 (33.5%)
Winter	101 (19.2%)
Parental smoking	
Yes	259 (49.2%)
No	267 (50.8%)
Size of histamine skin wheal (mm)	4.4 ± 1.1
Maximum diameter of positive allergen wheal (mm)	11.4 ± 6.2
Parental allergy history	
None	287 (54.6%)
Single	185 (35.2%)
Both	54 (10.3%)
Allergic sensitization	
Mono-sensitization	66 (12.5%)
Poly-sensitization	460 (87.5%)
Combined with asthma	
Yes	215 (40.9%)
No	311 (59.1%)

IAR: intermittent allergic rhinitis; PER: persistent allergic rhinitis.

3.2. Univariate analyses

Table 2 shows that the size of the histamine skin wheal and the maximal diameter of the positive allergen wheal displayed significant seasonal differences (P = 0.001 and P = 0.02, respectively). The children with biparental allergy history had higher BMI (P = 0.006).

3.3. Multiple linear regression analysis

As shown in Table 3, BMI (P < 0.001), summer testing (P = 0.001), and autumn testing (P < 0.001) were independently associated with the size of the histamine skin wheal, while age, type of allergic rhinitis, gender, parental smoking, parental allergy history, allergic sensitization, and asthma were not. Only winter testing was independently associated with the maximum diameter of the positive allergens (P = 0.002).

4. Discussion

There is an association between BMI and allergic diseases and bronchial hyper-responsiveness, but the factors influencing individual variations of histamine skin reactivity remain unknown.[9–12] Therefore, this study aimed to investigate the association between histamine skin reactivity and BMI and other clinical factors. The results showed that high skin reactivity to histamine was associated with high BMI. In addition, a novel finding of this study was that skin reactivity to histamine showed seasonal variation, with higher reactivity during summer or autumn. These associations should be considered for a better interpretation of the SPT.

The SPT is a reliable method for the diagnosis of allergic diseases involving IgE (asthma, allergic rhinitis, food allergies, and atopic dermatitis). Even if histamine is the usual standard positive control for SPT, it is essential to fully understand histamine skin reactivity to properly interpret the results of the SPT. Indeed, there are considerable variations in the skin reactivity to histamine among individuals,[4–8] but the reasons for these variations are not fully understood.

In the present study, the wheal size to histamine was positively associated with BMI in children of 3–6 years of age, as supported by two previous studies,[14,15] but no mechanism can be determined based on these results. Nevertheless, some possible explanations can be extracted from the available literature. Mast cells are critical actors involved in allergic reactions since they are the main source of histamine.[16,17] In addition, mast cells are associated with obesity.[16,17] Serum tryptase is used to assess the number and activity of mast cells and is positively associated with BMI.[18] Therefore, there is a possibility that the association between response to histamine and BMI could be mediated, at least in part, by the higher number and/or activity of mast cells due to obesity.

Of course, other factors and mechanisms could be involved in this association, such as skin fragility associated with higher BMI. Indeed, obese diabetic mice have higher skin fragility compared to normal mice.[19] In addition, skin blood flow increases with BMI, and obese individuals have increased skin redness after sodium lauryl sulfate stimulation.[20]

Previous reports showed that age, smoking, and atopy were associated with histamine skin reactivity,[4,21,22] but these observations are controversial.[23,24] Some studies showed a significant association between obesity and allergic responses. Bibi et al. reported that obese children

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Table 2 Univariate analyses of factors associated with BMI and histamine response.

Variables		BMI (kg/m^2)	P	Size of histamine skin wheal (mm)	P	Maximum diameter of positive allergen (mm)	P
Type of allergic rhinitis			0.172		0.768		0.232
IAR	202 (38.4%)	15.65 ± 1.28		4.43 ± 1.06		11.61 ± 5.86	
PER	164 (31.2%)	15.75 ± 1.23		4.35 ± 1.10		10.94 ± 6.30	
IAR + PER	160 (30.4%)	15.85 ± 1.3		4.39 ± 1.05		11.61 ± 6.61	
Gender							
Male	279 (53%)	15.8 ± 1.3	0.69	4.4 ± 1.1	0.465	11.5 ± 6.1	0.404
Female	247 (47%)	15.7 ± 1.2		4.4 ± 1.1		11.3 ± 6.4	
Season							
Spring	136 (25.9%)	15.9 ± 1.4	0.05*	4.1 ± 1.1	0.001*	10.7 ± 5.8	0.019*
Summer	113 (21.5%)	15.6 ± 1.2		4.5 ± 1.0		11.2 ± 6.4	
Autumn	176 (33.5%)	15.6 ± 1.2		4.6 ± 1.0		11.2 ± 6.1	
Winter	101 (19.2%)	16.0 ± 1.2		4.3 ± 1.2		13.0 ± 6.6	
Parental smoking							
Yes	259 (49.2%)	15.8 ± 1.3	0.434	4.4 ± 1.1	0.417	11.6 ± 6.0	0.111
No	267 (50.8%)	15.7 ± 1.3		4.4 ± 1.0		11.2 ± 6.5	
Parental allergy history							
None	287 (54.6%)	15.7 ± 1.3	0.006*	4.4 ± 1.1	0.536	11.8 ± 6.6	0.361
Single	185 (35.2%)	15.8 ± 1.2		4.5 ± 1.1		10.9 ± 5.5	
Both	54 (10.3%)	16.1 ± 1.2		4.5 ± 1.0		10.8 ± 6.5	
Allergic sensitization							
Mono-sensitization	66 (12.5%)	15.5 ± 1.2	0.109	4.5 ± 1.0	0.484	12.2 ± 6.9	0.378
Poly-sensitization	460 (87.5%)	15.8 ± 1.3		4.4 ± 1.1		11.3 ± 6.1	
Combined with asthma							
Yes	215 (40.9%)	15.7 ± 1.3	0.702	4.5 ± 1.1	0.202	11.6 ± 6.6	0.905
No	311 (59.1%)	15.8 ± 1.3		4.4 ± 1.1		11.3 ± 5.9	

BMI: body mass index; IAR: intermittent allergic rhinitis; PER: persistent allergic rhinitis. *$P < 0.05$.

had higher frequencies of asthma, wheezing, and inhaler use.[25] In addition, Peroni et al. reported that obesity was associated with asthmatic symptoms.[26] Chinn et al. reported that BMI and bronchial hyper-responsiveness were closely associated.[27] In an animal study, Malmlof et al. reported that histamine could play an important role in obesity, and that inhibiting the histamine receptor could decrease food intake, body weight, and plasma lipids.[28] Visnovsky et al. reported that age and body weight were related to histamine reactivity in the tracheopulmonary contractile tissues.[29]

The present study was not designed to determine the mechanisms leading to higher skin reactivity to histamine. Nevertheless, data suggest that histamine levels can be increased by the release of substance P, resulting in neurogenic inflammation.[30–32] Substance P is recognized as a target molecule for obesity.[33,34] Therefore, it could be hypothesized that increased levels of substance P in obesity could act as an allergic mediator through neurogenic inflammation, inducing greater histamine reactivity in obese patients.

The multiple regression analysis showed that testing during summer and autumn was associated with higher histamine reactivity, which could be associated with the presence of pollen in the air. Gamboa et al. reported that more histamine was released during spring and autumn than during the other two seasons.[35] Moreover, in China, summer is associated with the highest levels of humidity in the year. Autumn is associated with a change to drier weather. Therefore, in autumn, skin may become dryer and more vulnerable to external damage. Another possibility is that differences in the levels of inhaled allergens at various times of the year might contribute to seasonal variations in the histamine reactivity of the skin, particularly in people with IAR. A recent study of people with allergic rhinitis in north–east China has established the sensitization rates to a wide range of aeroallergens, including Dermatophagoides farinae (43.1%), Dermatophagoides pteronyssinus (38.8%), mugwort (33.6%), ragweed (29.0%), dandelion (28.3%), Blattella (23.5%), hazel (19.9%), birch (18.9%), goosefoot (14.9%), locust (13.8%), plantain (12.2%), grass pollen (9.4%), cereals (7.9%), animal dander (7.9%), Humulus (4.8%), Curvularia lunata (4.4%), Alternaria spp. (3.8%), pine (3.2%), Penicillum notatum (3.1%), and Aspergillus fumigatus (1.3%).[36] Further research is needed to establish whether seasonal changes in the levels of some of these inhaled allergens might influence the reactivity of the skin to histamine.

The present study has certain strengths. Indeed, race and age may influence histamine skin reactivity,[37] but the present study included children with the same ethnic background (Han Chinese). In addition, the seasonal variation of histamine reactivity was also analyzed in the present study.[5,7]

Nevertheless, the present study has several limitations. First, the sample size was too small to draw firm conclusions. Second, there are other possible variables (such as alcohol intake, stress levels, and circadian variations) that are associated with histamine skin reactivity.[38–40] Further

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Table 3 Multivariate analyses of variables associated with the allergic response.

Variables	Size of histamine skin wheal (mm)				Maximum diameter of positive allergen wheal (mm)			
	B	β	SE	P	B	β	SE	P
Age	0.016	0.017	0.041	0.692	0.059	0.01	0.246	0.812
BMI	0.196	0.234	0.036	<0.001*	−0.366	−0.075	0.218	0.093
Type of allergic rhinitis								
IAR								
PER	−0.111	−0.048	0.110	0.311	−0.818	−0.61	0.658	0.215
IAR + PER	−0.080	−0.034	0.109	0.466	0.139	0.10	0.657	0.833
Gender								
Male								
Female	−0.090	−0.042	0.091	0.324	−0.156	−0.013	0.545	0.775
Season								
Spring								
Summer	0.448	0.173	0.134	0.001*	0.424	0.028	0.803	0.597
Autumn	0.534	0.237	0.120	<0.001*	0.456	0.035	0.720	0.527
Winter	0.124	0.046	0.138	0.370	2.625	0.166	0.826	0.002*
Parental smoking								
Yes								
No	−0.066	−0.031	0.091	0.468	0.578	0.046	0.544	0.288
Parental allergy history								
None								
Single	0.055	0.025	0.098	0.577	−1.148	−0.088	0.591	0.052
Both	0.042	0.012	0.154	0.786	−1.050	−0.051	0.925	0.257
Allergic sensitization								
Mono-sensitization								
Poly-sensitization	−0.083	−0.026	0.138	0.549	−0.824	−0.44	0.827	0.320
Combined with asthma								
Yes								
No	0.096	0.044	0.092	0.296	0.205	0.016	0.553	0.711

B: unstandardized regression coefficient; β: standardized regression coefficient; BMI: body mass index; IAR: intermittent allergic rhinitis; PER: persistent allergic rhinitis; SE: standard error. Adjusted linear regression analysis was performed. *P < 0.05.

studies that include other possible variables may be needed. Third, we included patients with allergic symptoms rather than the general population. It is possible that different results would be observed in the general population. Nevertheless, the SPT is usually performed in patients who display allergic symptoms and not in the general population.

In conclusion, histamine skin reactivity increased with increasing BMI. Additionally, skin reactivity to histamine showed seasonal variation, with a greater response during summer or autumn. These associations should be considered for better interpretation of the SPT. Further studies regarding the mechanisms for these associations are needed.

Conflict of interests

All authors declare that they have no any conflict of interests.

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