

Sensitization pattern of inhalant allergens in children with asthma who are living different altitudes in Turkey

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Abstract Variability in children's allergic sensitization has been detected not only among different countries but also among cities within the same nation but yet different climatic areas. The aim of this study was to investigate the sensitization pattern of asthmatic children who lived in different altitude areas: the two largest Turkish cities, Istanbul (sea level) and Erzurum (high altitude). Five hundred and twelve asthmatic children (6–15 years old) from Istanbul (western Turkey, at sea level) and 609 from Erzurum (eastern Turkey, at an altitude of 1800 m) were included in the study. All participants underwent skin

testing with common inhalant allergens, spirometry, total IgE level, and clinical examination. The positive sensitization ratio to aeroallergens in children with asthma living at sea level was statistically higher than that in children living in the high altitude group [$p=0.001$, OR (odds ratio) 4.9 (confidence interval (CI) 3.67–6.459)]. However, pollen sensitization in asthmatic children living in high altitudes was significantly higher than that in children living at sea level [$p=0.00$, OR 2.6 (CI 1.79–3.87)]. Children with asthma who live at high altitudes are characterized by higher pollen but lower mite sensitization rates than those living at sea level in Turkey. Different climatic conditions and altitudes may affect aeroallergen sensitization in children with asthma.

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Introduction

Pediatric allergic diseases, such as bronchial asthma and allergic rhinitis, have been on the rise globally during the last three decades (Kusunoki et al. 2009; Civelek et al. 2011; Pearce et al. 2007). While the etiology of allergic disease is both genetic and environmental, sensitization to aeroallergens is mainly associated with environmental factors (climatic conditions, altitude, air pollution, temperature, humidity, etc.) (Sheffield et al. 2011; Valdivieso et al. 1999). The effect of aeroallergen sensitization on the development and symptoms of disease in childhood asthma is an important issue for

understanding future treatment options (Rijssenbeek-Nouwens et al. 2012; Rothe 2013).

Indoor allergen exposure and sensitization is an area of intensive ongoing research, whereas outdoor pollen, mold, and animal dander have been less investigated. As aeroallergens are sensitive to meteorological and topographical conditions, such as altitude, humidity, and temperature, a better understanding of the relationship between aeroallergen sensitization and symptoms in allergic disease in different outdoor climatic conditions is relevant. Concerning altitude, the climatic factor with the most effect on sensitization of aeroallergens is indoor relative humidity, which is lower at sea level (Njå et al. 2000). While some studies have explored indoor allergen sensitization in higher altitudes (Gourgoulisanis et al. 2001; Steen-Johnsen et al. 1995) and tropical environments (Montealegre et al. 2004), none included data to compare the aeroallergen sensitization pattern of asthmatic children who are living in different altitudes.

The objective of our study was to examine whether living at different altitudes may result in different allergic sensitization patterns when asthma has been taken into account.

Methods

Environmental and climatic conditions

The city of Istanbul is located at sea level in western Turkey. Istanbul, which connects Europe and Asia, has a transitional climate between a temperate Mediterranean climate and a temperate Oceanic climate with warm to hot and moderately dry summers and cool to cold and wet winters. The average summer (July) temperature is 27 °C (82 °F), and the average winter (January) temperature is 10 °C (50 °F). The average yearly temperature in Istanbul is around 19 °C with an average relative humidity of 76 %, mean rainfall of 787 mm, and mean wind speed of 3.2 m/s.

The city of Erzurum is the highest city in Turkey (latitude 39° 55', longitude 41° 16', altitude 1800–2000 m). Also, it is one of the cities with the lowest average temperature in Turkey. The climate is continental. Rainy springs, hot and dry summers, and cold and severe winters of long duration prevail in this area. From the data obtained at the airbase station between 1988 and 2013, the long-term mean temperature is 5.1 °C, the diurnal temperature range is 15.0 °C, the maximum temperature measured so far is 35.6 °C, and the minimum is −37.2 °C. Annual rainfall is 413.3 mm and the mean relative humidity is 63.3 % (Bulut et al. 2008).

Study population

This study was performed at the same time in Erzurum and Istanbul. Participants were enrolled in the authors' Pediatric Allergy-Pulmonology outpatient clinic between August 2011 and March 2013. All eligible subjects had a history of episodic shortness of breath, cough, chest tightness, wheezing, difficulty in expiration, and a documented history of reversibility of ≥ 12 % in FEV1 or of ≥ 15 % in peak expiratory flow within 15 min after inhaling salbutamol and being tested with dynamic spirometry. Patients who had additional clinical history of allergic rhinitis symptoms and who used allergic rhinitis treatment previously or actively were also included in the study. Diagnosis and severity of asthma were defined according to American Thoracic Society (ATS) guidelines (American Thoracic Society 1995). Subjects were 609 children (aged 6–15) from Erzurum and 512 children (aged 6–16) from Istanbul who had documented diagnoses of mild-to-moderate asthma and had been using inhaled corticosteroids. A study questionnaire requesting demographic data and family history of atopy was also obtained from each patient. Venous blood samples were taken from each patient and whole blood analysis and total serum IgE were measured.

Skin prick tests

A skin prick test was performed on the forearm of each patient using major allergens (Allergopharma, Germany). The same allergen extracts were used on all subjects. The allergens tested were a grass mixture (orchard grass, timothy grass, vernal grass, Kentucky blue grass, and rye grass), tree mixture (*Populus alba*, *Salix caprea*, *Olea europaea*, *Platanus vulgaris*, *Fraxinus excelsior*, and *Pinus silvestris*), cereal mixture (oat, wheat, barley, corn, and rye), weed mixture (mugwort, English plantain), mold and fungi mixture (*Alternaria*, *Aspergillus*, *Candida albicans*), cat and dog dander, cockroach (*Blattella germanica*), and house dust mites (HDM) (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*). Histamine dihydrochloride (10 mg/mL) and saline were used as positive and negative controls, respectively. The test was regarded positive if the average diameter of the weal was at least 3 mm greater than the negative control.

Statistical analysis

IBM SPSS software (v21, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. General characteristics were analyzed by an independent sample *t* test or by a Pearson chi-square test for category-wise data. The allergic sensitization type and rate of each city were compared by chi-square test. Binary logistic regression analysis was used in order to estimate the prevalence of aeroallergen sensitization according to the cities (Erzurum—high altitude, and Istanbul—sea level).

A p value <0.05 or OR (odds ratio) with a 95 % confidence interval (CI) that did not include zero was considered statistically significant.

Ethical approval

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the local ethics committee.

Results

The demographic and clinical parameters of the whole study population are shown in Table 1. The age of the high-altitude resident (Erzurum) children (mean age 8.6 ± 3.2 years) did not differ significantly from participating sea-level resident (Istanbul) children (mean age 9.3 ± 2.7 years). There were also no statistical differences between the two groups of patients with regard to sex, serum IgE levels, family history of atopy, disease severity, or pulmonary functions. Positive skin test ratio among the sea-level (Istanbul) and high-altitude (Erzurum) patients was 80.6 and 49.6 %, respectively. Sensitization against any of the tested allergens was statistically higher among the children living at sea level than those living at high altitude [$p=0.001$, OR 4.9 (CI 3.67–6.54)] (Table 2).

Grass mixture pollen sensitization in patients who lived at high altitude was significantly higher than that in patients who lived at sea level [$p=0.001$, OR 2.9 (CI 1.92–4.43)]. Tree mixture and cereal mixture sensitization in patients who lived at high altitude were also significantly higher than that in

Table 1 Comparison of patients' demographics and some clinical parameters according to the altitude level control

	Istanbul (sea level) $N=512$	Erzurum (>1800 m) $N=609$	p
Age mean, yrs	9.3 ± 2.7	8.6 ± 3.2	0.445
Male (%)	56	58	0.720
Duration of asthma (years)	4.5 ± 2.7	5 ± 3.2	0.578
Diagnosis			
Asthma (n , %)	142 (28)	159 (26)	0.312
Asthma and AR (n , %)	370 (72)	450 (74)	
Serum IgE levels (IU/mL)	305 ± 92	347 ± 119	0.440
Eosinophils/mm ³	375 ± 112	319 ± 86	0.290
FEV1 (% pred.)	89 ± 15	80 ± 16	0.670

The values represent the mean $\pm$ SD

AR allergic rhinitis, FEV1 forced expiratory volume in 1 s

Table 2 Association of the skin test positivity to aeroallergens with different altitude in children with asthma

Aeroallergen	Istanbul (sea level) $N=512$		Erzurum (>1800 m) $N=609$		OR (95 % CI) ^a	p
	n	%	n	%		
<i>D. pteronyssinus</i>	370	72.3	138	22.6	0.1 (0.07–0.13)	<0.001
<i>D. farinea</i>	365	71.3	145	23.8	0.1 (0.08–0.19)	<0.001
Grass mixture	38	7.5	120	19.7	2.9 (1.92–4.43)	<0.001
Tree mixture	20	4.0	61	10.1	6.7 (2.87–15.85)	<0.001
Cereal mixture	31	6.0	109	17.8	2.6 (1.79–3.87)	<0.001
Mold mixture	15	2.9	13	2.1	1.31 (0.90–1.90)	>0.05
Cat	13	2.5	17	2.8	1.16 (0.63–2.15)	>0.05
Dog	17	3.3	20	3.2	1.91 (0.67–5.49)	>0.05
Cockroach	19	3.7	13	2.1	0.60 (0.32–1.14)	>0.05
Total any positive	413	80.6	302	49.6	4.97 (3.67–6.54)	<0.001

^a Adjusted for gender, parental education, family history of atopy, serum eosinophils, total IgE, and the number of older siblings

OR odds ratio, CI confidence interval

patients who lived at sea level [$p=0.001$, OR 6.7 (CI 2.87–15.85), and $p=0.001$, OR 2.6 (CI 1.79–3.87), respectively] (Table 2). However, HDM sensitization in sea-level patients was significantly higher than that in high-altitude patients [$p=0.001$, OR 0.1 (CI 0.07–0.13)]. Sensitization to other common aeroallergens (mold, cat, dog, and cockroach) was not significantly different between the groups ($p>0.05$, Table 2).

Discussion

Our study demonstrated that the prevalence of allergen sensitization to pollen in high-altitude asthmatic children is higher than that in asthmatic children who are living at sea level. However, HDM sensitization in sea-level patients was significantly higher than that in their high-altitude peers. This study also showed that other indoor and outdoor allergic sensitization rates in asthmatic children were not statistically different between the two groups. In the present study, we compared, for the first time, the possible effects of different altitudes on aeroallergen sensitization in children with asthma. Our results suggested that living at a high altitude is an important risk factor in childhood asthma for pollen sensitization, especially tree pollens. Therefore, high altitude is a major determinant other than climatic conditions (e.g., temperature, humidity, and pollution) regarding pollen sensitization in children with asthma. Also, this study supports the idea that high altitude has a preventive effect on HDM sensitization.

Several elements may have contributed to the detection of a marked difference in the proportion of children sensitized to aeroallergens in the two groups. First, the percentage

of land considered to be forest or shrubbery in Erzurum (high altitude) is about 40 %, and 60 % is unsuitable for agriculture. The pollination period of trees and grasses starts at the end of March, continues until the end of September, and decreases in November. The pollen grains of these plants can reach high atmospheric concentrations most of the year. In contrast to Erzurum, in Istanbul (sea level), 20 % of the land is considered forest and shrubbery, 20 % is planted fields, and 40 % is suitable for agriculture. Pollination in Istanbul usually occurs in mid-spring and mid-autumn, intermittently, rather than persistently (Karaburun et al. 2010; Rijssenbeek-Nouwens et al. 2012). Second, the air pollution level may have an effect on allergen sensitization. According to measurements from the Ministry of Health, Erzurum is the most polluted province in the Eastern Anatolia Region (Bulut et al. 2008). The main reasons for air pollution are limited knowledge about burning techniques and use of low-quality coal rather than natural gas. Apart from those factors, the topographical situation of the city, irregular urbanization, and the increasing number of motor vehicles also have an effect on the increase of pollution (Karaburun et al. 2010; Nuhoglu et al. 2006). Average concentrations over the last 5 years of nitrogen oxide (NO), sulfur dioxide (SO₂), and particles are, respectively, 245, 307, and 221 µg/m³. Compare this to the recommended standards of the Environmental Protection Agency (EPA): SO₂=80 µg/m³, NO=100 µg/m³, and particles=75 µg/m³ (U.S. Environmental Protection Agency 2000). Air pollutant (SO₂, CO, NO, NO₂, NO) measurements in Istanbul, using data from air-quality measurement stations, showed decreases from 2002 to 2010 in the amounts of SO₂ (one of the main pollutants released as a result of the burning of fossil fuels) and CO (indicative of incomplete combustion). Average concentrations over the last 10 years of NO, SO₂, and particles were, respectively, 80, 30, and 22 µg/m³ (Yener and Koç 2006; Ozcan 2012). Air pollution may increase the expression of allergenic proteins, as plants release more pollen as a response to environmental threats (Suárez-Cervera et al. 2008). Also, components of air pollution may interact with aeroallergens carried by pollen grains, which results in sensitization (D'Amato et al. 2001; Cecchi et al. 2010). A study in four European cities showed that pollen allergens, β-glucans, and latex were bound to ambient air particles. As a result, combustion particles in ambient air can act as a carrier of allergens (Namork et al. 2006; Ziska et al. 2003). The impact of climate change on the pollen of common ragweed has also been assessed by Ziska et al., who used an existing CO₂/temperature gradient between rural and urban areas (2003). The higher CO₂ concentration of the urban area resulted in ragweed that produced significantly greater amounts of pollination. Additionally, increased ambient CO₂ may cause some plant products to become more allergenic, resulting in higher sensitization (Shea et al. 2008).

Changes in the start of the pollen season may also be associated with higher sensitization. In an early examination of the

potential impact of climate change on pollen seasons of allergy-causing plants in the European region, Emberlin (1994) showed that areas north of the Alps (higher than 2000 m) would have longer pollination seasons, as was observed in Erzurum in our study. Some reports also showed that prolonging of the pollen season and heavy snow (common in higher altitudes and affects some tree pollens) is associated with higher sensitization (Barne et al. 2013; Kenda et al. 1995).

Asthma in children in mild climates is often associated with mite sensitization (Cecchi et al. 2010). However, during the colder winter climates in Eastern Anatolia, especially Erzurum, more heat is used indoors, and this heated indoor air has low humidity. From Erzurum's weather data, it can be calculated that the relative humidity of the indoor air at 18–24 °C will normally never exceed 50 %. Experimental data has shown that below the critical equilibrium humidity (70 %), HDM can no longer survive, as their bodies progressively lose water and they succumb to desiccation (Brandt and Arlian 1976). Significant HDM exposure in such a setting is unusual, which explains why mite allergy is rare in these areas. Some reports also showed that areas with a high residence and a large temperature range between seasons are associated with less sensitization to mites (Spieksma et al. 1971; Nelson and Fernandez-Caldas 1995).

A nationwide study from Iran showed that HDM within the country are restricted to a small area close to the Caspian Sea, and therefore authors concluded that HDM were not an important risk factor for sensitization and respiratory allergy (Fereidouni et al. 2013). In that study, dust samples obtained from seven cities throughout Iran with different geo-climatic conditions were measured only for HDM concentration level. However, there is no further information about patient-oriented sensitization rates and HDM concentration as related to different altitudes.

The relative humidity of the indoor air itself is not the only factor affecting the growth of HDM. Another factor that contributes to the humidity conditions within houses is the type of construction and materials used. In Erzurum, most of the buildings and houses were constructed of natural stone and superficial soil, which do not allow penetration of water and temperature from the outside to the inside. This structure style maintains a high relative humidity and an inadequate environment for the growth of mites.

High altitude alone may not be the only factor of mite sensitization. Valdivieso and Iraloa (2011) showed that high altitude (2800 m above sea level) in the tropics is not a major determinant for the presence of HDM. This report suggested that other climatic conditions, such as temperature and humidity, are factors for dust mite growth. From a clinical standpoint, Murray et al. (1985) showed that skin prick tests for HDM were positive in 40 % of those asthmatic children from the high-humidity area, whereas in those children from

dry areas, tests were 2 % positive. There was also a marked difference in the degree of sensitivity.

Available data suggests that the dose-response relationship between allergen exposure and allergic disease may differ between different allergens (Weinmayr et al. 2007), dose ranges, and exposure patterns, and the relationship may further differ between different populations (Zeldin et al. 2008) and geographical areas. It is increasingly clear that childhood asthma and atopy are not single phenotypes, and it is likely that allergen exposure has a different effect on different subtypes. However, the precise nature of these complex relationships is unclear (Custovic 2014). Our aim in this study was simple in that it only explored the sensitization patterns of asthmatic children who lived at different altitude levels rather than including indoor and outdoor allergen particle concentration and sensitization patterns. For this reason, we did not measure indoor and outdoor allergen particle counts.

Conclusion

Our study unveiled a high prevalence of skin sensitization to pollens, but not other aeroallergens, in asthmatic children residing in high altitudes. The co-existence of high altitude and low humidity may be an important risk factor for sensitization to pollens in these children. Traits that are traditionally put forward to back up the importance of climatic factors in allergic sensitization (i.e., high altitude, humidity) may result in different sensitization patterns.

Conflict of interest All of the authors declare that they have all participated in the design, execution, drafting, interpretation of data, and analysis of the study and approve the final version of the paper. The authors have no financial or personal relationships with other people or organization that could pose a conflict of interest in connection with the present work.

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