



The association of residential mold exposure and adenotonsillar hypertrophy in children living in damp environments



Ozlem Atan Sahin ^{a,*}, Nuray Kecicioglu ^b, Muhittin Serdar ^c, Aysel Ozpinar ^c

^a Acıbadem University School of Medicine, Department of Pediatrics, İstanbul, Turkey

^b Acıbadem Eskişehir Hospital, Tepebaşı, Eskişehir, Turkey

^c Acıbadem University School of Medicine, Department of Biochemistry, İstanbul, Turkey

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ABSTRACT

Background: There are many consequences of mold exposure related to respiratory system health of children. This retrospective cohort study aims to find the association between adenoid hypertrophy and mold exposure in children living in damp environments.

Methods: Children with history of recurrent respiratory tract infections were enrolled in the study between June 2012 and June 2013 and were followed up for adenoid hypertrophy from June 2013 to June 2016. One hundred and forty two children were residents of moldy houses and 242 were living in normal houses. Skin prick test results for 60 common allergens, vitamin D levels, IgE levels, age, presence of comorbidities such as urticaria, atopic dermatitis, allergic conjunctivitis, allergic rhinitis, asthma, frequency of upper respiratory tract infections and lower respiratory tract infections, were evaluated in both groups.

Results: A total of 384 children (mean age $\pm$ standard deviation = 53.37 ± 36 months; 198 males and 186 females) were included. The children were classified into 2 groups (1) Children living normal houses ($n = 242$) (2); Children living in damp houses ($n = 142$) according to mold exposure. Children with adenoid hypertrophy ($p < 0.001$) and higher IgE levels ($p < 0.001$) were more common in mold exposed group. Lower respiratory tract infections were more common in children with mold exposure ($p < 0.05$). Bivariate correlation analysis showed no significant association between IgE levels and adenoid hypertrophy. Multiple linear regression analysis was performed to evaluate IgE levels, vitamin D levels, and presence of adenoid as independent variables; age as dependent variable among two groups and was found statistically significant ($p < 0.001$). Dermatophagoid sensitive group living in damp houses had a significant increase in adenoid hypertrophy ($p = 0.01$). House dust mite sensitive children with recurrent lower respiratory tract infection and upper respiratory tract infection were mainly residents of damp houses ($p < 0.001$). Allergic comorbidities were significantly more in damp environment group ($p < 0.001$), but there was no significant increase in any of the subgroups.

Conclusions: Children with mold exposure had significantly increased adenoid hypertrophy regardless of their atopic nature, however, they may have become more sensitized due to other environmental triggers and genetic factors. In damp environments, sensitization to dermatophagoids, was significantly increased in children with adenoid hypertrophy. During the period of infancy, when children were mostly vitamin D supplemented, they were not sensitized and had normal adenoids. As children with recurrent respiratory tract infections grow, they tend to have lower vitamin D levels, become more atopic and tend to have adenoid hypertrophy.

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1. Introduction

Respiratory infections in children remain a major cause of morbidity and mortality in developing countries. Children are more vulnerable to indoor air pollution levels because they have a higher minute ventilation and are more physically active. Adenoid

* Corresponding author. Acıbadem University School of Medicine, Department of Pediatrics, Kerem Aydınlar Kampüsü, Kayışdağı cad. No. 32, 34752, Ataşehir, İstanbul, Turkey.

E-mail address: ozlemnaciyeatansahin@yahoo.com (O. Atan Sahin).

hypertrophy (AH) is a common disorder with prevalence of 2–3%. Adenoids are very small in newborns but tend to grow during infancy through the first 4 years of life as immune system develops. Adenoid hypertrophy can occur with a wide spectrum of symptomatology such as nasal obstruction, nasal and post nasal discharge, snoring, ear ache, decreased hearing, sleep apnea and asthma attacks [1]. There is evidence that AH may be associated with respiratory and cardiovascular morbidity. It may have major effect on quality of life and healthcare costs [2]. Children with adenoids are more prone to oxidative stress [3]. Exposure to mold has been linked to frequent lower respiratory tract infection (LRTI) in atopic individuals, and emerging data suggest that mold might trigger the development of asthma [4,5]. Patients with adenoids experience frequent LRTI. Therefore, the objective of this retrospective study is to rule out the association of mold exposure, vitamin D levels, IgE levels with adenoid hypertrophy and to rule out if adenoids are an independent risk factor, like atopy for LTRI. All data and samples that belong to patients used for this study were collected during routine clinical care in an outpatient setting. (see Fig. 1).

2. Methods

2.1. Data extraction

Admissions to department of pediatrics between June 2012 and June 2013 were evaluated retrospectively. 384 children (198 male, 186 female, between 12 and 202 months, mean $\pm$ SD, 55.6 ± 6 months) with history of recurrent respiratory tract infections and available data including; skin prick test results, vitamin D levels, IgE levels, age, gender, routine clinical examination data that belong to the pediatrician and otorhinolaryngologist fulfilled the eligibility criteria. 384 children with previous laboratory data and without adenoid hypertrophy were selected from hospital records retrospectively. The past records of children beginning from June 2013, until January 2016 were evaluated for development of adenoid hypertrophy. Evaluation and diagnosis of adenoid hypertrophy was performed by ear nose and throat specialist based on history, endoscopic and radiological examination. The 142 children were living in damp terrace houses in subtropical climate and 242 were living in normal houses with dry climate. Damp house residents live in Bodrum, in southwest coast of Turkey while children with

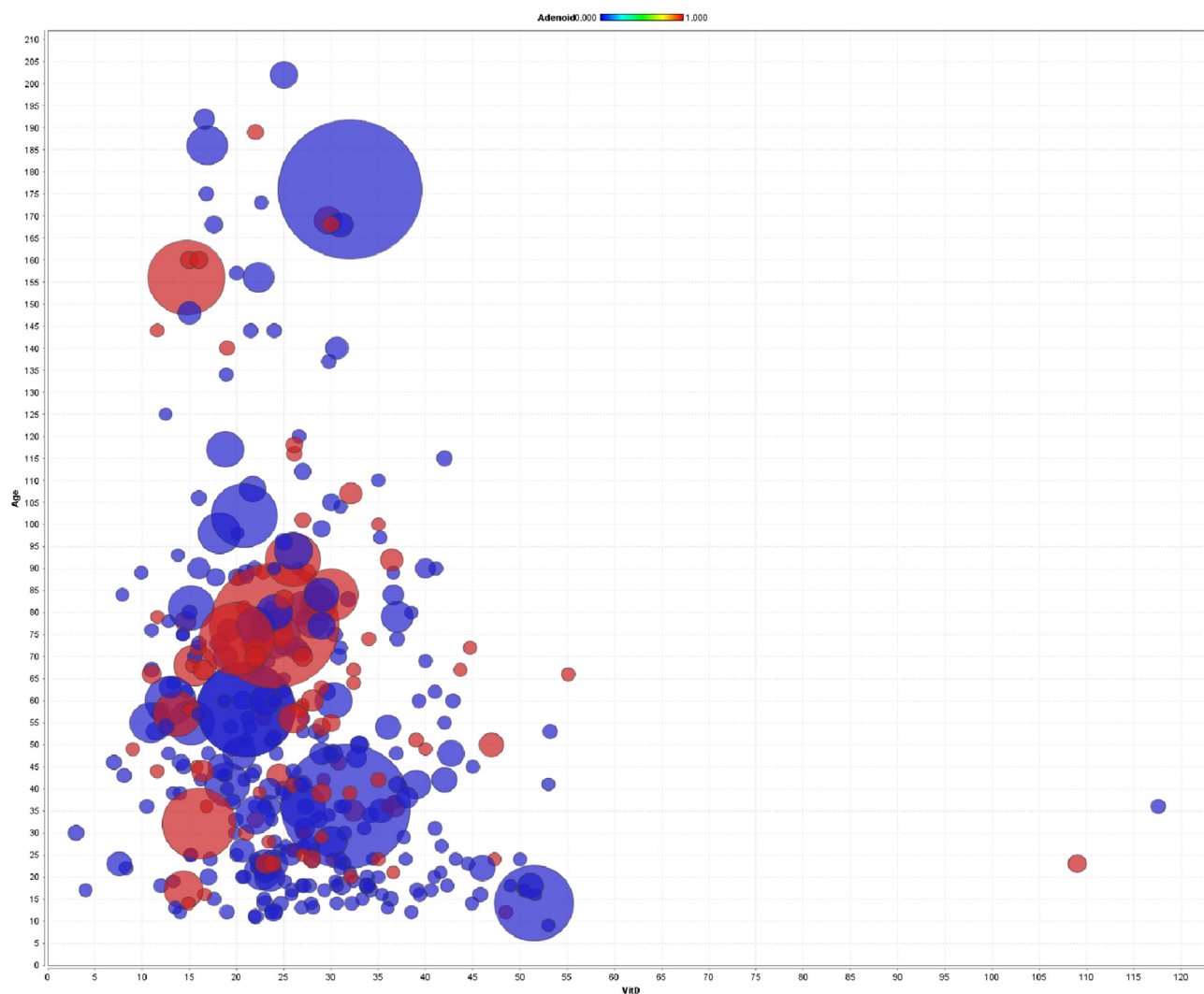


Fig. 1. Correlations of age and vitamin D, IgE, presence of adenoids in damp and normal houses. x-axis: Vitamin D level. y-axis: Age. Blue colour: cases with adenoid hypertrophy. Red colour: cases without adenoid hypertrophy. Size of Bubbles: IgE level. Bivariate correlation analysis was used to determine IgE level, vitamin D level and adenoid hypertrophy relationship, and results indicated that it was not statistically significant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dry household live in Middle Anatolia region. The dampness of the household was documented by a standard mold exposure questionnaire that parents or caregivers of the study population were asked [6]. Children of parents who answered all questions 'yes' were included in the study as mold exposed group. All of the children had previously been evaluated with skin prick tests (Alyostal ST-IR, Stallergenes S.A France) for 60 common allergens which are, *Aspergillus mix* (*Aspergillus Fumigatus*, *A. Nidulans*, *A. Niger*), *Cladosporium cladosporioides*, *C. Herbarum*, *Penicillium Mix* (*Penicillium DigitatuBodrumm*, *P.Expansum*, *P. Notatum*), *Alternaria Alternata*, *Rhizopus Nigricans*, *Mucor racemosus*, *P.Purpureogenum*, *P.Crustosum*, *P.Spinulosum*, *P. Corylophilum*, *D. pteronyssinus*, *D.Pharinae*, storage mites (*Acarus siro*, *Glyciphagus domesticus*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*), *Paspalum Notatum*, *Hordoleum Vulgare*, *Agrostis Vulgaris*, *Cynodon dactylon*, *Weed Mixture*, *Zea Mays*, *Festuca eliator*, *Poa pratensis*, *Avena Sativa*, *Secale Cereale*, *Lolium Perenne*, *Anthoxantum Odoratum*, *Phleum Pratense*, *Triticum Vulgare*, *Holcus Lanatus*, 4 cereals (oat, wheat, barley, maize), *Sambucus nigra*, *Taraxatum Vulgare*, *Chenopodium Album*, *Artemisia Vulgaris*, *Urtica Doica*, *Chrysanthemum Leucanthemum*, *Lantanago*, *Ambrosia Eliator*, *Salsola Cali*, *Rumex Acetosa*, *Parietaria Officinalis*, *Rough Pigweed*, *Golden Rod*, *Almus Glutinosa*, *Fraxinus Excelsior*, *Fagus Sylvatica*, *Betula Alba*, *Castena Vulgaris*, *Juniperus Ashesi*, 5 Grasses, *Olea europea*, *Ulmus Campestris*. Vitamin D levels, IgE levels, age, presence of comorbidities such as urticaria, atopic dermatitis, allergic conjunctivitis, allergic rhinitis, asthma, frequency of URTI and LRTI were evaluated in both groups. They had at least two visits at otorhinolaryngologist and at least 8 visits at pediatrician office for recurrent respiratory tract infections. Evaluation and diagnosis of adenoid hypertrophy was performed by ear nose and throat specialist based on history, endoscopic and radiological examination. Patient information was anonymized and de-identified prior to analysis. Ethics committee approval for this study was obtained from Kecioren Research Hospital Ethics committee.

2.2. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) Version 18.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Continuous data are expressed as, means $\pm$ standard deviation, and categorical data are presented as frequencies (percents). The one-way ANOVA test followed by a posthoc test (Bonferroni) was used to compare the age and vitamin D level, IgE level and adenoid existence. Mann Whitney *U* test was used to analyze and compare IgE, 25-OH vitamin D levels, URTI, LRTI, allergic comorbidities such as, urticaria, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, skin prick test results, pollen, mite and mold sensitivities of two groups. Multiple regression analysis was used to rule out the associations between age as dependent, vitamin D levels, existence of adenoids, IgE levels as independent variables. A statistical significance was considered to be reached at *p*-value <0.05. (see Fig. 2).

3. Results

176 (45%) of the study group were female, and 208 (55%) were male. 142 (36%) of the cases were residents of moldy homes, while 242 (64%) cases were residents of normal homes. IgE, 25-OH vitamin D levels, URTI, LRTI, allergic comorbidities such as, urticaria, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, skin prick test results, pollen, mite and mold sensitivities among two groups are demonstrated Table 1.

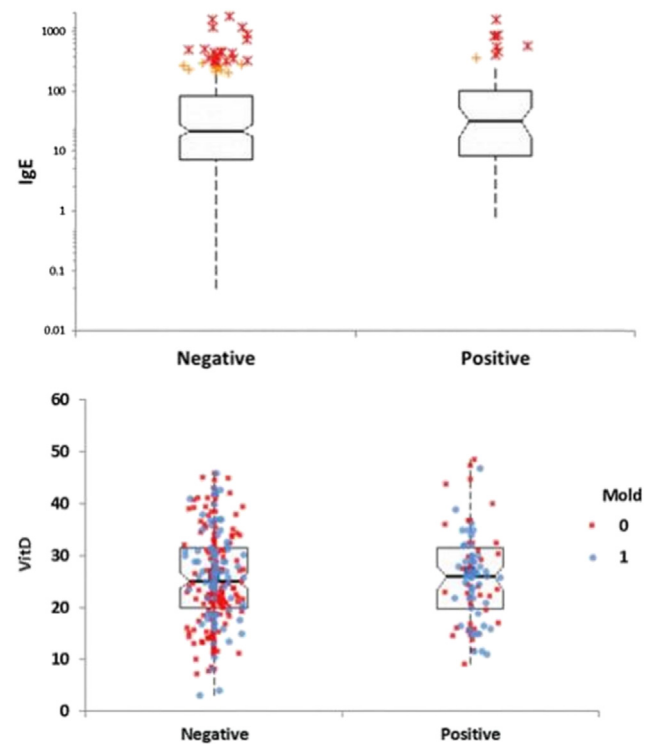


Fig. 2. Association of IgE and vitamin D level in adenoid positive and adenoid negative children. x -axis: Adenoid negative and positive patients. y -axis: IgE and vitamin D levels. Blue colour: cases living in moldy homes. Red colour: cases living in normal homes. Existence of comorbidities in adenoid (+) and adenoid (–) groups in different residential settings were demonstrated in Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Adenoidectomy is the second most common surgical procedure performed in pediatric otorhinolaryngological practice [7]. Despite conventional and new techniques, complications of surgery are, injury to eustachian tube orifice and pharyngeal musculature, bleeding and high percentage of remaining residual tissue, have been mentioned in previous studies [8,9]. Allergenic and infectious stimuli are main triggers of adenoid hypertrophy in susceptible children.

The recognition that societies spend an increasing amount of their lives indoors, has attracted researchers interest in indoor environment [10]. House insulation is maintained to decrease heat loss. As a result air circulation becomes so limited that indoor moist, allergens and irritants increase. In cold climates mold exposure is around 5%–30%, while it is twice as much in tropical and hot environments [11,12]. Low vitamin D levels have been linked to increased incidence of upper respiratory tract infections and adenotonsillar disease [13,14]. In literature optimum 25(OH)D levels, vary from 16 to 60 ng/ml in different ethnic populations [15–18]. Variation in optimum 25 (OH) vitamin D may partially be explained by differences in ethnicity, age, gender, vitamin D receptor polymorphisms and assays used. In our study residents of subtropical and damp environment had higher vitamin D levels than dry residential setting as expected.

The development of atopic disease occur in a number of discrete phases: induction, progression and exacerbations of acute episodes. One of the best known indoor allergen is housedustmite [19]. Once the induction phase begins, inflammatory response and airway hyperreactivity are induced by environmental agents which will

Table 1

Adenoid hypertrophy, URTI, allergic disorders, atopy status, prick positivity, mold, pollen and dermatophagoid sensitivities of damp and normal house residents.

	Normal house (n = 242)	Damp house (n = 142)	Total (n = 384)	P value
Adenoid(–)	198	90	288	$P < 0,001$
Adenoid(+)	44	52	96	
URTI (+)	179	93	272	$P > 0,05$
URTI (–)	63	49	112	
LRTI (+)	77	59	136	$P < 0,05$
LRTI (–)	165	83	248	
VitaminD deficient	123	46	169	$P < 0,001$
Vitamin D sufficient	118	96	214	
High IgE (–)	202	89	291	$P < 0,001$
High IgE (+)	40	53	93	
Prick (–)	224	90	314	$P < 0,001$
Prick(+)	18	50	68	
Allergic disorders (+)	34	27	61	$P < 0,05$
Allergic (–) disorders	208	115	323	
Pollen (–)	233	117	350	$P < 0,001$
Pollen(+)	7	25	32	
Mold(–)	235	118	353	$P = 0,002$
Mold(+)	7	15	22	
Dermatoph.(–)	232	114	346	$P < 0,001$
Dermatoph.(+)	10	28	38	

There was statistically significant difference among vitamin D levels of the two groups. Vitamin D deficiency was significantly less in residents of subtropical environment as expected. Individuals with high IgE levels were mainly residents of moldy homes ($p < 0,001$). Adenoid hypertrophy was present in 54.2% of residents of moldy homes ($p < 0,05$). In moldy home residents, LRTI frequency was 41%, ($p < 0,05$). URTI frequency did not differ significantly among the two groups. Fifty-six children in the mold exposed group had at least one positive skin prick test result. 22 were only housedustmite sensitive, 22 were only pollen sensitive, 8 were only mold sensitive, 4 cases were polysensitized to pollen, mite and mold at the same time. 50 out of 68 pricktestpositive patients were residents of moldy homes ($p < 0,001$). Out of 38 dermatophagoid sensitized children, 28(73%) were damp house residents ($p < 0,001$), out of 22 mold sensitized children 15(68%)were residents of damp houses($p < 0,001$) and out of 32 pollen sensitized children 25(78%) were damp house residents($p < 0,001$). Out of 96 children with adenoids, 8 were Dermatophagoid sensitized and all of them were residents of damp houses, ($p = 0,001$).

Age and vitamin D levels were negatively correlated, while age and IgE levels were positively correlated. Multiple linear regression analysis indicated a significant relationship between age as dependent variable and IgE levels, vitamin D levels, adenoid hypertrophy as independent variables ($p < 0,001$).

Table 2

General characteristics of children with comorbidities and adenoids.

Other allergic disorders		Adenoid (–)	Adenoid (+)	Total	P value
None	Normal household	170 (52,6%)	38 (11,8%)	208 (64,4%)	$P < 0,05$
	Damp house	72 (22,3%)	43 (13,3%)	115 (35,6%)	
	Total	242 (74,9%)	81 (25,1%)	323 (100%)	
Urticaria	Normal household	3 (50)%	1 (16,7)%	4 (66,7)%	$P > 0,05$
	Damp house	1 (16,7)%	1 (16,7)%	2 (33,3)%	
	Total	4 (66,7)%	2 (33,3)%	6 (100)%	
Eczema	Normal household	14 (73,7)%	2 (10,5)%	16 (84,2)%	$P > 0,05$
	Damp house	3 (15,8)%	0 (0)%	3 (15,8)%	
	Total	17 (89,5)%	2 (10,5)%	19 (100)%	
Conjunctivitis	Normal household	1 (50)%	0 (0)%	1 (50)%	$P > 0,05$
	Damp house	0 (0)%	1 (50)%	1 (50)%	
	Total	1 (50)%	1 (50)%	2 (100)%	
Rhinitis	Normal household	7 (31,8)%	3 (13,6)%	10 (45,5)%	$P > 0,05$
	Damp house	9 (40,9)%	3 (13,6)%	12 (54,5)%	
	Total	16 (72,7)%	6 (27,3)%	22 (100)%	

There was no significant difference among two residential settings for allergic comorbidities as demonstrated. 1,4% percent of all patients with urticaria were residents of moldy homes, and 0,8% were residents of normal homes. 16 patients (84,2%), out of 19 patients with eczema, were residents of moldy homes. One of 2 patients with allergic conjunctivitis was a resident of moldy environment. Eleven (47%) patients out of 23 with allergic rhinitis, lived in moldy houses.

trigger exacerbations and/or progression of inflammation resulting in allergenic phenotype [20]. Published data suggest that developmental pattern of immune system in early life is strongly associated with external stimuli. Genetic susceptibility, exposure to environmental allergens and different environmental conditions play the major role in disease phenotype. Asthma is more prevalent in cities than rural areas [21].

The epidemiological data of 60 out of 142 children who are damp house residents had previously been published in our preliminary study [22]. Our pre-eliminary study, and other studies regarding observations on increased asthma attacks due to mold exposure in atopic individuals, do not indicate a significant presence of mold hypersensitivity. It is suggested that mold may cause sensitization via non IgE mediated pathways. Clinical effects of

mold exposure are due to three most common causes; allergy, infection and toxicity. The airborne particles of bacteria and molds are generally unstable and show great variances due to the lack of eligible assessment and analysis techniques [23].

High IgE levels may be associated with parasitic disease, some viral infections, atopic nature while normal IgE levels do not exclude atopy. Accurate diagnosis should be based on examination findings, specific IgE levels and skin prick tests, however, for diagnosis of allergic rhinitis, provocation test is the mainstay in diagnosis, while skin prick tests and IgE levels may be normal. This may be one of the limitations of our study as it is difficult to perform provocation tests in all pediatric ages. Another limitation may be the questionnaire for documentation of exposure had been selected for its hard to measure exposures with available measuring

techniques [24].

In our study, residents of Bodrum (damp environment); have always lived in seaside of Mediterranean, a subtropical climate. The results revealing high IgE levels in our patients, may be attributed to the higher pro-Th2 allele frequency in populations of tropical and subtropical origin compared with those from higher latitude in Turkey. Available data suggest that Th-2 biased responses in tropical climates are due to the ancestors inherited responses against helminthic parasites and that these parasites are more common in moist and hot climates. Children with tropical ancestry also have greater risk of infections due to inadequate response to immunization and also adenoids are mostly observed in immune compromised children with low IgG levels; as a result these children will eventually have impaired ability to limit airway inflammations. In a retrospective study involving 87 children with partial IgA and/or IgG subclass deficiency, 24% have been found to have high IgE levels as in our study. These children were residents of Aegean coast of Turkey [25]. In our study, children living in damp and subtropical region had significantly more LRTIs, adenoids, higher IgE, higher mold, pollen and dermatophagoid sensitizations. Children with adenoids, living in damp residential environments only demonstrated dermatophagoid sensitization. The reason for this may be, microbial burden that modulate the developmental patterns of the immune system. Previous studies about early age exposures to increased amount of endotoxins, molds and bacterial products have conflicting results [26–29]. According to the results of our study, children living in damp environments are probably more atopic; and also have limited capability to limit infections due to genetic factors. One interesting finding in our study is that, dermatophagoid sensitization was significantly higher than mold sensitization in children with mold exposure and adenoid hypertrophy. This may also indicate that different immunological pathways may play a role in sensitization to different aeroallergens.

In our study there was no significant correlation between IgE levels and development of adenoid hypertrophy. Children with adenoids living in damp houses had frequent LRTI. Post nasal drainage, or immune defects due to moldy air may cause a significantly increased LRTA in damp environments. In our opinion, when LRTI is observed in a child with adenoid hypertrophy living in damp environment, dermatophagoid sensitivity should be ruled out. In the study of Huang S, it was demonstrated that children with allergic rhinitis and mold allergy were more susceptible to development of adenoid hypertrophy however in our study no significant correlation was found [30]. Our study revealed increased sensitization rates for molds, pollen and dermatophagoids in residents of damp environment, while children with adenoids living in damp environments were sensitized to dermatophagoids significantly. This also supports the idea that mold sensitivity detection rates may be low for aforementioned reasons while dermatophagoids which share similar environmental conditions as molds may seem to cause easier sensitization. Atopic children were more prone have LRTI, rather than URTI and they were mainly residents of damp houses. Twin studies have shown that nearly half of asthma occurrences are inherited suggesting that disease phenotype is modulated significantly by environmental factors. The reason for considerable variance in responsiveness to these exposures may be explained by genetic factors. Polymorphisms of Toll-like receptor (TLR-2) modulate the degree of protection against allergic diseases [31,32]. Among residents of moldy homes with higher IgE levels but less allergic phenotypes in children with adenoid hypertrophy, such polymorphisms may display antagonistic effects. As an explanation to less sensitization than expected, specific fungi sensitization may sometimes be necessary for the induction of polysensitization in moldy environments as indicated in another study [33]. In another birth cohort, statistically significant increase

in asthma risk at age 7 years was associated with high Environmental Moldiness Index value in childrens' home during infancy [34]. Our study population mostly consisted of younger children and that would be one of the reason for insignificant asthma rates for mold exposed group. Another reason may be that it is hard to diagnose infantile asthma; so some of the children with LRTI may indeed be infantile asthma cases, and this may be one of the limitations of our study.

In the study of Zielnik-Jurkiewicz B et al. [35], atopic and non atopic children with chronic otitis media had high proinflammatory cytokine levels (TNF –alfa, IL-1beta, IL-6 and IL-8), and anti-inflammatory management regardless of atopy status was suggested. As susceptible children may demonstrate different patterns of sensitization in different environments, studies regarding mechanistic features of inflammation in different environmental conditions should be encouraged for evidence based management of anti-inflammatory therapies in the future. In another study, Th17/Treg balance was increased on the OSA (obstructive sleep apnea) patients with allergic rhinitis, indicating that this balance could be modified to restore immune homeostasis [36]. In another study, there was no association between OSA and adolescents with metabolic syndrome without adenoid hypertrophy [37]. These may be examples to how different phenotypes or disease patterns can occur under influence of regulatory mechanisms or metabolic states. In our study group, none of the patients with and without adenoid hypertrophy exhibited OSA or metabolic syndrome findings. However, they exhibit different outcomes due to environmental conditions. Topical or oral treatment options are suggested in children with adenoids in various studies and anti-inflammatory medications have changed the size of adenoids in children significantly in selected studies [38–40]. Children who are residents of damp and hot climates are generally atopic in nature and when they are exposed to allergens or irritants, they become susceptible individuals for LRTIs.

In conclusion, a new potential consequence of tropical climate and mold exposure in damp environments may be adenoid hypertrophy in susceptible individuals which had not been indicated in previous studies. Remediation of damp homes might mitigate some cases of asthma attacks, LRTI, adenoid hypertrophy and consequently reduce adenoidectomy. Children living in damp environment should closely be monitored for probable LRTIs, especially the ones with adenoid hypertrophy. Early detection of adenoids would protect children from frequent LRTI's and its complications. Despite optimum vitamin D levels in children living in subtropical regions, children are prone to develop adenoid hypertrop in mouldy residential settings. As number of studies increase on mechanistic influences of environmental factors on innate and adaptive immune systems during childhood, the influence of multipotential program of cytokine production, determining the nature of immune response to external stimuli will be understood better.

Conflict of interest

None.

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