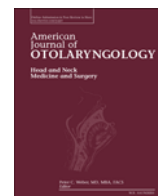




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Inhalant allergen sensitization is an independent risk factor for the development of angioedema

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ABSTRACT

Background/objective: The etiology and risk factors for angioedema remain poorly understood with causative triggers often going undiagnosed despite repeated reactions. The purpose of this study was to determine the relationship between inhalant allergen sensitization and angioedema.

Methods: A retrospective review of patients who had in vitro inhalant allergy testing from 2006 to 2010 was performed. Patients with a diagnosis of angioedema who underwent inhalant allergy testing were identified. Analyses for co-morbidities, class of sensitization, seasonal timing of angioedema, and concurrent use of known hypertensive medications that can cause angioedema were performed.

Results: There were 1000 patients who underwent inhalant allergy testing and qualified for the study. 37/1000 had at least one episode of angioedema and of these patients, 34 had positive inhalant sensitization testing results. Multivariate regression models showed overall sensitization status, seasonal allergen and epidermal/mite sensitization as independent risk factors ($p < 0.001$, $p = 0.005$, $p = 0.025$ respectively) when controlling for ACE inhibitor use and other covariates. Tree, and epidermal/mite sensitizations were independent risk factors for angioedema in mono-sensitized subject analysis ($p = 0.028$, $p = 0.029$, respectively).

Conclusion: Both seasonal and perennial allergen sensitizations are independent risk factors for the development of angioedema. In patients with angioedema and an unknown trigger, inhalant allergen sensitization should be considered as a potential contributing factor to the development of angioedema.

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1. Introduction

Angioedema is a serious reaction characterized by an acute onset of localized edema of the subcutaneous and submucosal tissue from an increase in vascular permeability mediated by vasoactive agents [1]. Angioedema often requires immediate evaluation by multiple healthcare providers and at times critical airway intervention on the part of otolaryngologists, allergists, emergency medicine physicians and anesthesiologists. It is a rare cause of death with an incidence of 0.1–2.2%, yet it is commonly treated in the emergency setting and often requires significant resources for hospitalization [2–4]. Although numerous

studies have reported on angioedema, the causes are poorly understood [5,6].

Angioedema has been classified into two major groups, acquired and hereditary [2]. Hereditary is often recurrent and related to a C1-esterase inhibitor deficiency [7]. The other classifications include angiotensin converting enzyme inhibitor (ACE-I) related, idiopathic histaminergic and idiopathic non-histaminergic [1,7]. A recent retrospective analysis of 1058 patients with angioedema found that ACE-I related angioedema made up 17% of the cohort while idiopathic histaminergic and non-histaminergic comprised a combined 42% [3]. These groups, however, are often related and there can be continued recurrent angioedema events of unknown etiology despite discontinuation of ACE-I use [8]. Since angioedema is related to type I hypersensitivity reactions, this study was completed to better determine the relationship between common inhalant allergen sensitizations and angioedema.

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2. Material and methods

IRB approval, study number H-33251, was obtained at Boston University Medical Center. Patients were identified for inclusion in the study if they had undergone in vitro sensitivity testing at a single tertiary academic medical center between 2006 and 2010. Allergy testing was performed by ELISA (ImmunoCap, Phadia, Sweden) for 29 inhalant allergens. Several patients had repeated visits for testing of which their sensitization data were combined. The final study sample comprised of 1046 encounters of which 1000 individual patients qualified.

Retrospective chart review was then completed identifying demographics including age, sex, ethnicity, and hypertension status determined by patients' use of hypertensive medications including ACE-I, beta-blockers, thiazides and calcium channel blockers (CCB). Initial use or duration of hypertensive medications was not included due to chart review restrictions. Allergen sensitizations were recorded for individual inhalant allergens and also organized by class (trees, grasses, weeds, molds, epidermal/mites). Epidermal allergens were defined as cat and dog sensitizations. Mites were defined as dermatophagoides farinae and dermatophagoides pteronyssinus sensitizations. Class of allergen sensitization was assigned to a season; i.e., trees = spring (March, April, May), grasses = summer (June, July, August), weeds = fall (September, October, November). Mold, epidermal and mite sensitizations were designated as perennial and therefore not associated with any specific season. Finally, the season of each angioedema event was determined based on the date of diagnosis. The type of angioedema and location of edema were not included in the study since not all patients were examined at the single institution during their angioedema episode and due to variation in clinical documentation.

A set of multivariate logistic regression models was used to assess whether allergen sensitization was a risk factor for angioedema. The first model used an indicator of any allergen sensitization as the main independent predictor of angioedema (Model 1). The second model disentangled the main predictor into sensitization to seasonal allergens and sensitization to perennial allergens (Model 2). The third model further separated the predictor into five major allergen classes as the main predictors of angioedema (Model 3). Because the estimates in Model 2 and Model 3 could suffer from multicollinearity due to an association among the main predictors (poly-sensitization), a sensitivity analysis was performed by restricting the sample to individuals who were sensitized only to the particular group or class of allergens of interest or not sensitized at all. All multivariate models were adjusted for age, gender, ethnicity, and the use of ACE inhibitors. Models were also adjusted for the diagnosis of asthma, nasal polyposis and the use of other hypertensive medication besides ACE inhibitors when possible (restrictions were due to sample size and the consequent lack of degrees of freedom). The same set of three multivariate analyses were stratified by hypertension status in order to understand if hypertensive patients had similar risk factors compared to non-hypertensive patients.

To determine the effect of seasonal occurrence on angioedema, it was hypothesized that angioedema is equally likely to occur in each of the four seasons among those with no allergen sensitization and those with only perennial allergen sensitization, whereas angioedema is more likely to occur during the appropriate allergy season ("in-season") rather than during the other seasons ("off-season") among those with seasonal allergens sensitization. To test these hypotheses, a unit of analysis, one "person-season", allowed for control of the different length of exposure for mono-sensitized and poly-sensitized patients. This analysis describes the number of seasonal opportunities a patient has during the study period to have an angioedema event during the season of their associated allergen sensitization. The sample comprised of 20,000 person-seasons (1000 individuals followed for 20 seasons). For each person-season, it was noted whether the individual was sensitized to allergens associated with the particular season. Chi-squared tests (or Fisher's exact tests when appropriate) were performed to assess the association between season and angioedema events among those with

no allergen sensitization and among those with perennial but no seasonal allergens sensitization. Finally, a multivariate logistic regression model was completed with angioedema as the outcome and an indicator of the appropriate allergy season as the main predictor using the subsample of individuals with seasonal allergen sensitization. This model also controlled for season, perennial allergens sensitization, age, gender, ethnicity, diagnosis of asthma and the use of various hypertensive medications. Because perennial allergen sensitization might have confounded the estimates, the authors fitted the same model also to a subsample restricted to individuals with seasonal but no perennial allergen sensitization.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina). A level of statistical significance was set as $\alpha = 0.05$.

3. Results

A total of 1000 patients, predominantly comprised of African American (29.5%), Caucasian (29.0%) and Hispanic (22.5%) patients were included in the study (Table 1). The majority of subjects were females (59.8%). Over the five-year study period, the observed average annual rate of angioedema was 7.4 per 1000 individuals, which is in line with the generally reported incidence rate [2,4,9], >60% patients tested positive to at least one allergen. Being sensitized to an allergen from a major allergen class was significantly associated with being sensitized to an allergen from another major allergen class (Fig. 1). Analogously, sensitization to seasonal allergens was significantly associated with sensitization to perennial allergens (OR = 7.47, $p < 0.001$, Supplemental Table A1).

Table 2 summarizes the results of multivariate logistic regression models for angioedema risk factors when looking at all patients. All three models confirmed the existing knowledge that older patients, African Americans and ACE inhibitor users are at increased risk of angioedema. Model 1 showed that individuals with at least one allergen sensitization had significantly increased odds of angioedema (OR = 9.32, $p < 0.001$). When stratifying the sample by hypertensive status

Table 1
Demographics.

	Mean	SD
Age	37.1	15.9
	n (N = 1000)	%
Male	402	40.2%
Ethnicity		
°African American	295	29.5%
°Asian	70	7.0%
°Hispanic	225	22.5%
°White	290	29.0%
°Other	70	7.0%
°n/a	50	5.0%
Asthma	241	24.1%
Hypertensive medication use ^a	231	23.1%
°ACE inhibitor	82	8.2%
°Beta blockers	100	10.0%
°Calcium channel blockers	61	6.1%
Nasal polypos	109	10.9%
Positive inhalant in vitro	604	60.4%
Sensitization to at least one allergen ^b	603	60.3%
°Sensitization to at least one seasonal allergen ^c	409	40.9%
°°Sensitization to trees (spring)	333	33.3%
°°Sensitization to grasses (summer)	228	22.8%
°°Sensitization to weeds (fall)	250	25.0%
°Sensitization to at least one perennial allergen ^d	515	51.5%
°°Sensitization to mold	121	12.1%
°°Sensitization to epidermal allergens/mites	491	49.1%
Total number of angioedema cases (over 5 years)	37	

^a Some patients were using more than one hypertension medication.

^b Sensitization to at least one allergen from the following list: trees, grasses, weeds, mold, epidermal allergens, mites.

^c Seasonal allergens: trees, grasses, weeds.

^d Perennial allergens: mold, epidermal allergens, mites.

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