

# Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center

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**Background:** Although acute allergic reactions after ingestion of peanuts and tree nuts are common, fatalities are rare. Other than patients with coexisting asthma, it is currently not possible to predict which patients are most likely to develop severe reactions. **Objective:** The aim of this study was to determine which clinical and laboratory parameters best predict the likelihood of severe allergic reactions.

**Methods:** From 1992 to 2004, we collected detailed information on the clinical severity and allergy test results of 1094 patients with peanut and tree nut allergy attending a regional allergy center. In a subgroup of 122 patients, sera were assayed for activity of enzymes involved in the catabolism of bradykinin.

**Results:** Severe pharyngeal edema was 3.8 (2.1-6.9) times more common in patients with severe rhinitis and 2.6 (1.8-3.7) more common after ingestion of tree nuts compared with peanuts.

Patients with serum angiotensin-converting enzyme concentrations <37.0 mmol/L had a 9.6 (1.6-57)-fold risk of severe pharyngeal edema. Life-threatening bronchospasm was most likely in patients with severe asthma (relative risk, 6.8 [4.1-11.3]) and less so in patients with milder asthma (2.7 [1.7-4.0]). Altered levels of consciousness were more likely in patients with severe eczema (3.1 [1.1-8.4]).

**Conclusion:** Severity of coexisting atopic diseases predicted which patients attending a tertiary referral clinic were most likely to develop life-threatening allergic reactions to peanuts and tree nuts. Patients with the lowest serum angiotensin-converting enzyme concentrations were more likely to develop life-threatening pharyngeal edema, suggesting that this complication may be partly mediated by bradykinin. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

**Key words:** Anaphylaxis, tree nuts, peanut, atopy, asthma, ACE, aminopeptidase P, bradykinin, age

## Abbreviations used

ACE: Angiotensin-converting enzyme

APP: Aminopeptidase P

SPT: Skin prick test

UK: United Kingdom

Peanut and tree nut allergy is common, with a prevalence of around 1% to 1.3% of the population.<sup>1-3</sup> It is a growing perceived if not real concern in the Western world.<sup>4,5</sup> However, the risk of death from allergic reactions is very small, occurring in less than 1 in a million people.<sup>6-9</sup> If it were possible to predict which patients were at risk of developing severe allergic reactions, these few patients could be more effectively targeted with, for instance, emergency treatment kits including injectable epinephrine devices, whereas the remainder could have their fears allayed and treatment restricted to education and avoidance measures. Unfortunately, most life-threatening/fatal anaphylactic reactions are unpredictable, and recommendations on the management of patients with peanut and tree nut allergy remain largely based on opinion rather than randomized clinical trials.<sup>10-12</sup>

Over a period of 12 years in a single regional allergy unit, we carefully documented the severity of allergic reactions in 1094 patients with these allergies. The type of nut, the severity of associated atopic diseases (eczema, asthma, and hay fever), standard allergy tests results (allergen-specific serum IgE concentrations and skin prick tests [SPTs]), and, in a subgroup of patients, serum angiotensin-converting enzyme (ACE) and aminopeptidase P (APP), enzymes involved in the breakdown bradykinin, one of the major mediators of anaphylactoid reactions,<sup>13</sup> were documented and compared to determine which factors predicted patients who had life-threatening allergy symptoms after ingestion of peanuts and tree nuts. This study describes not only the factors that will and will not predict the severity of allergic reactions but also the type of symptoms the patient is most likely to experience.

## METHODS

### Patients

In the 12 years between 1992 to 2004, clinical details as well as, in many cases, total and allergen specific serum IgE concentrations and SPT results of all individuals with peanut and tree nut allergy attending regional pediatric and adult allergy clinics at Manchester Royal Infirmary, Manchester, United Kingdom (UK), were recorded on structured history forms. Copies of the completed forms were kept with the patient records, and all data were entered into a Microsoft Access (Microsoft UK, Reading, UK) database (Manchester Allergy Research Database). Patients having blood taken for IgE measurements had serum stored in a centralized serum bank. The collection of this

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**TABLE I.** Classification of severity of allergic symptoms and atopic diseases in patients with peanut and tree nut allergy and frequency of patients with these symptoms

| Symptoms                                                        | No symptoms | Mild                                                     | Severe                                                       |
|-----------------------------------------------------------------|-------------|----------------------------------------------------------|--------------------------------------------------------------|
| Potentially life-threatening                                    |             |                                                          |                                                              |
| Pharyngeal edema                                                | 626 (57%)   | 184 (17%)                                                | 284 (26%)                                                    |
|                                                                 |             | Hoarse                                                   | Drooling/dyspnea                                             |
| Bronchospasm                                                    | 686 (63%)   | 224 (20%)                                                | 164 (15%)                                                    |
|                                                                 |             | Not requiring hospital                                   | Requiring hospital                                           |
| Reduced conscious level suggestive of circulatory insufficiency | 937 (86%)   | 124 (11%)                                                | 33 (3%)                                                      |
|                                                                 |             | Faint/dizzy                                              | Unconscious                                                  |
| Non-life-threatening                                            |             |                                                          |                                                              |
| Angioedema                                                      | 339 (31%)   | 668 (61%)                                                | 87 (8%)                                                      |
|                                                                 |             | Lips/face                                                | Generalized                                                  |
| Urticaria                                                       | 447 (40%)   | 291 (27%)                                                | 356 (33%)                                                    |
|                                                                 |             | Localized                                                | Generalized                                                  |
| Atopic disease                                                  |             |                                                          |                                                              |
| Eczema                                                          | 419 (38%)   | 474 (44%)                                                | 201 (18%)                                                    |
|                                                                 |             | Mild topical steroids only                               | More potent topical steroids                                 |
| Asthma                                                          | 515 (47%)   | 386 (35%)                                                | 193 (18%)                                                    |
|                                                                 |             | Never hospitalized                                       | Required hospital                                            |
| Rhinitis                                                        | 704 (65%)   | 311 (28%)                                                | 79 (7%)                                                      |
|                                                                 |             | Controlled with oral antihistamines and topical steroids | Not controlled with oral antihistamines and topical steroids |

Values are the number (percentage) of patients with these symptoms.

information and serum had the approval of the Local Research Ethics Committee (04/Q1401/44).

Data on the clinical severity of allergic reactions were recorded from 1094 patients with nut allergies (872 patients in whom the most severe reaction was to peanut and 222 patients in whom the most severe reaction was to tree nut). The diagnosis was made on the basis of a physician's clinical history, supported by either evidence from SPTs or raised allergen specific serum IgE concentrations. Clinical symptom severity was scored for each of a number of symptoms as detailed in Table I. The mean number of reactions patients had experienced was 3; for the purposes of this study, the record of the most severe reaction was analyzed. As well as these physical symptoms, patients were scored as to whether they had a feeling of impending doom/fear of dying (panic) at the time of their most severe allergic reaction.

A subset of 122 patients for whom sufficient serum had been stored in the serum bank, 46 of whom at a history of moderate to severe pharyngeal edema, 36 who had moderate to severe bronchospasm, and 40 with no history of these symptoms, had their ACE and APP concentrations measured as detailed.

## Serum IgE measurements

Total serum IgE concentrations were measured by fluoroimmunoassay using an automated Phadia ImmunoCap 1000 immunoassay processor (Phadia Ltd, Milton Keynes, UK).

## SPTs

Skin prick tests were performed where clinically indicated by using standardized reagents to almond, brazil nut, cashew nut, hazelnut, peanut, pine nut, and walnut (ALK-Abelló, Hungerford, UK). Standardized histamine reagent was used as a positive control. No patient had taken any oral antihistamines for at least 5 days before testing. The reaction was recorded as the size of wheal in millimeters after 15 minutes. Both serum IgE measurements and SPT results used in analysis were those closest in time, generally within 3 months of the clinical reaction.

## Serum ACE assay

Angiotensin-converting enzyme concentrations were performed according to the manufacturer's instructions by using standardized 300 ACE calorimetric

assay kits purchased from Alpha Laboratories Ltd, Eastleigh, UK. Specificity of the assay was checked by the ability of captopril (Biochemika, Gillingham, UK) to block enzyme activity completely.

## Serum aminopeptidase P (APP) assay

Aminopeptidase P assay with bradykinin 1-3 (Bachem Ltd., Merseyside, UK) as the substrate was performed using the colorimetric method previously described.<sup>14</sup> Specificity of the assay was checked by the ability of apstatin (Tebu-bio, Peterborough, UK) to block enzyme activity completely.

## Statistical analysis

Data from the centralized Access database were entered into an SPSS spreadsheet (SPSS Inc., Chicago, Ill) for the purposes of analysis. Because some of the data were not normally distributed (age, total and allergen specific serum IgE concentrations, SPT wheal, serum ACE and APP concentrations), continuous variables are quoted as median (interquartile range). Comparison between groups was performed by using  $\chi^2$  analysis for discrete variables, and for continuous variables, the Mann-Whitney test (for 2 independent groups) or Kruskal-Wallis test (for more than 2 independent groups). Multivariate analyses were performed by using binary logistic or Cox regression analysis, and results are described as odds ratios (95% CIs). *P* values are always quoted for 2-tailed analysis.

## RESULTS

### Demographic information and severity of acute allergic reactions to peanuts and tree nuts

Data from 1094 patients with a history of allergic reactions to peanuts and tree nuts who were seen in a single regional allergy referral center in Manchester, UK, were analyzed. A total of 573 (52%) patients were male. A total of 831 (76%) were children between 1 month and 15 years of age, and the remaining 263 adults were 16 to 70 years old. The median (interquartile range) age of the entire cohort was 6 (2-15) years. A total of 874 (80%) patients had their most severe allergic reaction to peanut and the remainder

to tree nut (cashew nut, 79 [7%]; brazil nut, 74 [7%]; walnut, 35 [3%]; hazelnut, 21 [2%]; almond, 6 [1%]; pine nut, 5 [1%]).

After ingestion of peanuts or tree nuts, 413 (37%) of patients developed only urticaria or angioedema involving the skin or lips, but no pharyngeal edema, bronchospasm, or reduced consciousness. In contrast, 468 (43%) of patients developed symptoms of pharyngeal edema on at least 1 occasion (206 [19%] without ever any associated bronchospasm or reduced consciousness); 388 (35%) had symptoms of bronchospasm (159 [15%] without any pharyngeal edema or reduced consciousness); and 157 (14%) had reduced consciousness (23 [2%] without any pharyngeal edema or reduced consciousness; Table I; see this article's Table E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). A total of 341 patients developed severe pharyngeal edema, bronchospasm, and/or reduced consciousness, and in 192 (62%), this was their first allergic reaction to nuts.

In the overall cohort, 17 patients had diabetes, and 4 had hypertension. Eight patients were on  $\beta$ -blockers, 3 were on ACE inhibitors, and 6 were on antidepressants (selective serotonin reuptake inhibitors or tricyclics). Within the subcohort analyzed in relation to ACE and APP, only 2 patients were on  $\beta$ -blockers, 1 patient was on an ACE inhibitor, and no patients were on antidepressants. These factors were not associated with severity of acute allergic symptoms on univariate and multivariate analysis.

### Clinical factors predicting the severity of allergic reactions

Adults were more likely to experience severe pharyngeal edema (odds ratio [95% CI], 3.7 [2.6-5.2]), bronchospasm (2.0 [1.3-3.1]), and particularly reduced consciousness (8.9 [3.9-20.0]) than children. Severity of allergy symptoms did not differ significantly by sex.

The association between severity and type of acute allergic reactions and chronic atopic disease (eczema, asthma, or rhinitis) was investigated by using multivariate analysis to control for any confounding effect of age (Table II). The presence of atopic diseases affecting the upper or lower airways or skin was associated with severe allergic symptoms affecting the upper and lower airways and systemic circulation, respectively. The strongest predictor of severe upper airway obstruction was severe atopic disease affecting the upper airway (allergic rhinitis; 3.8 [2.1-6.9]), whereas the strongest predictor of severe lower airway disease was severe atopic disease affecting the lower airway (asthma; 6.8 [4.1-11.3]), and the strongest predictor of allergic disease affecting the systemic circulation was severe atopic dermatitis/eczema (3.1 [1.1-8.4]). In contrast, a history of allergic rhinitis was not associated with reduced consciousness, and a history of eczema was not associated with either severe upper or lower airway obstruction.

Symptoms of pharyngeal edema (severe upper airway obstruction) were 2.6 (1.8-3.7)-fold more common after ingestion of tree nuts than peanuts ( $P < .0001$ ). In contrast, angioedema not affecting the upper airway and other allergic symptoms (bronchospasm, reduced consciousness, urticaria) were not more common after ingestion of tree than peanuts.

### Laboratory factors predicting the severity of allergic reactions and atopic disease

Total and specific serum IgE concentrations were significantly higher in patients with more severe atopic disease. Although on univariate analysis there was an association between total serum

**TABLE II.** Multivariate analysis examining the association between the severity and type (upper respiratory tract, lower respiratory tract, systemic) of acute allergic reactions and the severity of chronic atopic disease in the total cohort of 1094 patients (831 [76%] of whom were children)

| Severe allergy symptoms          | Atopic disease           | Odds ratio (95% CI) | P value |
|----------------------------------|--------------------------|---------------------|---------|
| Upper airway (Pharyngeal edema)  | Upper airway             |                     |         |
|                                  | Mild rhinitis            | 2.4 (1.7-3.3)       | <.001   |
|                                  | Moderate-severe rhinitis | 3.8 (2.1-6.9)       | <.001   |
|                                  | Lower airway             |                     |         |
|                                  | Mild asthma              | 0.8 (0.6-1.1)       | .2      |
|                                  | Moderate-severe asthma   | 1.6 (1.0-2.5)       | .04     |
|                                  | Systemic                 |                     |         |
|                                  | Mild eczema              | 0.9 (0.6-1.3)       | .6      |
|                                  | Moderate-severe eczema   | 0.8 (0.5-1.2)       | .3      |
|                                  | Age                      |                     |         |
| Lower airway (Bronchospasm)      | Adults vs children       | 3.7 (2.6-5.2)       | <.001   |
|                                  | Upper airway             |                     |         |
|                                  | Mild rhinitis            | 1.2 (0.8-1.9)       | .3      |
|                                  | Moderate-severe rhinitis | 2.1 (1.2-4.0)       | .02     |
|                                  | Lower airway             |                     |         |
|                                  | Mild asthma              | 2.7 (1.7-4.2)       | <.001   |
|                                  | Moderate-severe asthma   | 6.8 (4.1-11.3)      | <.001   |
|                                  | Systemic                 |                     |         |
|                                  | Mild eczema              | (0.6-1.5)           | .9      |
|                                  | Moderate-severe eczema   | 1.2 (0.7-1.9)       | .6      |
| Systemic (Reduced consciousness) | Age                      |                     |         |
|                                  | Adults vs children       | 2.0 (1.3-3.1)       | .002    |
|                                  | Upper airway             |                     |         |
|                                  | Mild rhinitis            | 0.5 (0.2-1.2)       | .1      |
|                                  | Moderate-severe rhinitis | 0.5 (0.1-1.9)       | .3      |
|                                  | Lower airway             |                     |         |
|                                  | Mild asthma              | 0.9 (0.4-2.2)       | .9      |
|                                  | Moderate-severe asthma   | 2.0 (0.8-5.2)       | .2      |
|                                  | Systemic                 |                     |         |
|                                  | Mild eczema              | 1.6 (0.6-4.1)       | .3      |
|                                  | Moderate-severe eczema   | 3.1 (1.1-8.4)       | .03     |
|                                  | Age                      |                     |         |
|                                  | Adults vs children       | 8.9 (3.9-20.0)      | <.001   |

Binary logistic regression analysis. Acute allergy symptoms after ingestion of nuts (patients with symptoms were compared with patients with no symptoms) were the dependent variables. Chronic atopic disease (moderately-severe, mild, no disease [reference group]), and age at time of reaction (adults vs children) were covariants.

IgE and severity of acute bronchospasm after eating peanuts and tree nuts, multivariate analysis demonstrated that this could be accounted for entirely by the strong correlation between acute bronchospasm and chronic asthma symptoms (data not shown). Thus, overall in this cohort there was no significant association between serum total and specific IgE concentrations and severity of allergic symptoms. There was also no association between skin prick wheal size and either severity of chronic atopic diseases or acute allergic reactions (Table III).

Patients with severe pharyngeal edema had significantly lower serum ACE concentrations (39 [33-51] mmol/L) than those with no pharyngeal edema (47 [40-59] mmol/L;  $P = .01$ ; Table IV; see this article's Fig E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). None of the patients were on ACE inhibitors. Using multivariate analysis (binary logistic regression) to control for any confounding effects of age, sex, and atopic diseases, patients with serum ACE concentrations in the lowest quartile (<37.0 mmol/L) were 9.7 (1.6-57) times more likely to have severe pharyngeal edema

**TABLE III.** Total and allergen-specific serum IgE concentrations as well as SPT wheal size in patients grouped on the basis of severity of allergic reaction (pharyngeal edema, bronchospasm, reduced consciousness) or atopic disease (allergic rhinitis, asthma, or eczema)

|                            | Nil          | Mild           | Severe         | P value |
|----------------------------|--------------|----------------|----------------|---------|
| Total serum IgE (KIU/L)    |              |                |                |         |
| Pharyngeal edema           | 400 (80-822) | 450 (75-1100)  | 425 (90-900)   | .8      |
|                            | 477          | 147            | 230            |         |
| Bronchospasm               | 340 (75-800) | 450 (90-900)   | 650 (130-1700) | <.001   |
|                            | 530          | 191            | 135            |         |
| Reduced consciousness      | 400 (80-900) | 475 (80-900)   | 500 (90-1950)  | .5      |
|                            | 731          | 98             | 25             |         |
| Rhinitis                   | 300 (65-800) | 600 (155-1085) | 700 (192-1400) | <.001   |
|                            | 549          | 244            | 64             |         |
| Asthma                     | 220 (55-700) | 450 (90-925)   | 900 (400-4500) | <.001   |
|                            | 394          | 306            | 157            |         |
| Eczema                     | 240 (60-700) | 380 (80-800)   | 800 (380-2200) | <.001   |
|                            | 319          | 383            | 155            |         |
| Specific serum IgE (KIU/L) |              |                |                |         |
| Pharyngeal edema           | 14 (2-80)    | 16 (2-75)      | 7 (1-46)       | .1      |
| Bronchospasm               | 7 (1-55)     | 19 (3-90)      | 32 (5-180)     | <.001   |
| Reduced consciousness      | 11 (2-75)    | 19 (2-75)      | 36 (3-140)     | .7      |
| Rhinitis                   | 11 (2-89)    | 13 (2-75)      | 5 (1-38)       | .2      |
| Asthma                     | 6 (1-46)     | 16 (2-82)      | 27 (5-298)     | <.001   |
| Eczema                     | 7 (1-75)     | 10 (2-70)      | 26 (3-100)     | .005    |
| SPT wheal (mm)             |              |                |                |         |
| Pharyngeal edema           | 7 (5-10)     | 8 (6-10)       | 7 (5-10)       | .2      |
|                            | 430          | 121            | 184            |         |
| Bronchospasm               | 7 (6-10)     | 7 (5-10)       | 8 (5-11)       | .4      |
|                            | 456          | 174            | 106            |         |
| Reduced consciousness      | 7 (5-10)     | 8 (5-10)       | 6 (4-12)       | .8      |
|                            | 642          | 79             | 14             |         |
| Rhinitis                   | 7 (5-10)     | 7 (6-10)       | 7 (6-10)       | .7      |
|                            | 486          | 205            | 45             |         |
| Asthma                     | 7 (5-10)     | 8 (6-10)       | 9 (5-10)       | .2      |
|                            | 322          | 271            | 143            |         |
| Eczema                     | 7 (5-10)     | 7 (6-10)       | 8 (5-10)       | .4      |
|                            | 231          | 365            | 140            |         |

Results are displayed as medians (interquartile ranges). The number in each group is given below the median (numbers in IgE and specific IgE groups are the same). Kruskal-Wallis H test was used to determine 2-tailed *P* value. The allergy test result relates to the nut that caused the clinical allergic reaction.

(*P* = .01) than patients with higher ACE levels (Table V). There was a similar trend for patients with angioedema not involving the pharynx, but this did not reach significance. In contrast, severe bronchospasm, reduced consciousness, and urticaria were no more likely in the quartile with the lowest serum ACE concentrations. Serum APP concentrations did not vary significantly with severity of allergy symptoms, and multivariate analysis comparing patients with APP in the lowest quartile with the rest of the cohort did not show any significant trends for any parameter of clinical allergy severity.

### Determinants of psychological symptoms after acute allergic reactions

Symptoms of panic were 2.3 to 2.4 times more common in patients with severe upper airway obstruction or patients with severe bronchospasm than in patients with no symptoms. Panic reactions were 3 times more common in adults than children and 1.7 times more common in female subjects than male subjects.

## DISCUSSION

This study clearly demonstrates the strong link between symptoms of peanut and tree nut-induced acute allergic reactions

and chronic atopic disease involving the upper airway and lower airway and more generalized systemic effects. A history of severe rhinitis was associated with a 4-fold risk of severe pharyngeal edema, severe asthma with a 7-fold risk of acute bronchospasm, and severe eczema with a 3-fold risk of becoming unconscious during an acute allergic reaction. These associations were independent of age and sex. Age of the patient was another important factor predicting the severity of allergic reactions, with adults 2 to 9 times more likely to develop severe reactions than children. The study highlights the fact that it is not so much the presence or absence of coexisting chronic atopic diseases that is important in predicting the likelihood of life-threatening acute allergic reactions, but rather the severity of these atopic diseases.

These results contrast with previous, largely anecdotal reports summarizing cases of fatal allergic reactions, which suggested that patients with any degree of asthma (mild to severe) may be at a higher risk of life-threatening allergic reactions.<sup>15,16</sup> One implication of our findings is that good asthma control may prevent life-threatening acute bronchospasm after ingestion of nuts, although there may be little effect on the severity of other symptoms of anaphylaxis such as pharyngeal edema. The strong association between symptoms of acute bronchospasm after nut ingestion and a history of severe asthma (*P* < .0001) suggests

**TABLE IV.** Serum ACE and APP concentrations in patients grouped on the basis of severity of acute allergic reaction (pharyngeal edema, bronchospasm, reduced consciousness) or chronic atopic disease (allergic rhinitis, asthma, or eczema) in a subgroup of 122 patients

|                       | Nil           | Mild          | Severe        | P value |
|-----------------------|---------------|---------------|---------------|---------|
| ACE (mmol/L)          |               |               |               |         |
| Pharyngeal edema      | 48 (40-58)    | 52 (39-66)    | 39 (33-51)    | .02     |
|                       | 56            | 20            | 46            |         |
| Bronchospasm          | 46 (37-53)    | 55 (40-69)    | 43 (36-60)    | .1      |
|                       | 72            | 14            | 36            |         |
| Reduced consciousness | 47 (38-56)    | 41 (35-56)    | 45 (35-47)    | .4      |
|                       | 95            | 18            | 9             |         |
| Angioedema            | 47 (38-58)    | 45 (36-55)    | 40 (31-55)    | .5      |
|                       | 44            | 66            | 12            |         |
| Urticaria             | 45 (36-53)    | 47 (39-53)    | 45 (36-59)    | .8      |
|                       | 39            | 35            | 48            |         |
| Rhinitis              | 46 (37-53)    | 46 (40-59)    | 49 (31-66)    | .8      |
|                       | 73            | 32            | 17            |         |
| Asthma                | 45 (37-53)    | 47 (36-53)    | 45 (38-64)    | .8      |
|                       | 51            | 37            | 34            |         |
| Eczema                | 47 (38-59)    | 45 (35-53)    | 46 (38-56)    | .9      |
|                       | 45            | 54            | 23            |         |
| APP (mU/mL)           |               |               |               |         |
| Pharyngeal edema      | 2.4 (1.7-4.4) | 3.2 (1.4-4.9) | 3.7 (1.7-6.2) | .3      |
| Bronchospasm          | 2.9 (1.9-5.8) | 2.4 (1.6-3.8) | 2.5 (1.3-5.0) | .3      |
| Reduced consciousness | 2.8 (1.7-5.1) | 2.6 (1.9-4.3) | 2.7 (1.0-6.8) | .9      |
| Angioedema            | 2.5 (1.5-3.7) | 3.7 (1.8-5.8) | 3.6 (1.9-6.9) | .1      |
| Urticaria             | 3.7 (2.0-6.2) | 2.9 (2.1-4.7) | 2.6 (1.4-4.2) | .2      |
| Rhinitis              | 2.9 (1.6-5.0) | 2.4 (1.5-4.5) | 3.7 (2.2-6.8) | .2      |
| Asthma                | 2.9 (1.8-5.8) | 2.6 (1.5-4.8) | 2.7 (1.6-4.7) | .8      |
| Eczema                | 2.7 (1.5-4.5) | 3.3 (1.7-5.9) | 2.9 (1.7-4.9) | .6      |

Results are displayed as median (interquartile range) concentrations, and number in each group is given below the median (numbers in APP group are the same as for the ACE group). Kruskal-Wallis H test was used to determined 2-tailed *P* value.

**TABLE V.** Association between severity of allergy symptoms and low serum ACE concentration (serum ACE in the lowest quartile, <37.0 mmol/L)

|                       | Nil         | Mild           | Severe         | P value |
|-----------------------|-------------|----------------|----------------|---------|
| Pharyngeal edema      | 7/55 (13%)  | 4/18 (22%)     | 18/43 (42%)    | .004    |
|                       | 1.0         | 4.4 (1.1-16.7) | 9.6 (1.6-58.0) | .01     |
| Bronchospasm          | 19/68 (28%) | 2/14 (14%)     | 8/24 (24%)     | .5      |
|                       | 1.0         | 0.7 (0.2-2.5)  | 1.0 (0.1-7.4)  | .8      |
| Reduced consciousness | 20/91 (22%) | 6/17 (35%)     | 3/8 (38%)      | .4      |
|                       | 1.0         | 1.1 (0.2-7.0)  | 0.9 (0.1-6.8)  | 1.0     |
| Urticaria             | 12/36 (33%) | 6/35 (17%)     | 11/45 (24%)    | .3      |
|                       | 1.0         | 0.7 (0.2-2.4)  | 1.1 (0.3-4.1)  | .8      |
| Skin angioedema       | 7/42 (17%)  | 16/61 (26%)    | 6/13 (46%)     | .1      |
|                       | 1.0         | 1.4 (0.3-7.6)  | 2.0 (0.5-8.8)  | .6      |

Results are displayed as number (percentage) and *P* value determined by  $\chi^2$  statistical analysis. Below these values are odds ratios (95% CIs) using patients with no symptoms as a reference. Odds ratios and associated *P* values were calculated by using binary logistic regression with age, sex, and atopic diseases as covariates.

that they have a common pathophysiological mechanism. If this is indeed the case, then allergic reactions to nuts predominantly associated with symptoms of acute bronchospasm may be as effectively managed using evidence A and B–based guidelines for acute severe asthma<sup>17</sup> as with current opinion-based recommendations promoting the use of intramuscular epinephrine devices.

Risk factors leading to severe pharyngeal edema were found to differ from those associated with severe bronchospasm. Severe allergic rhinitis and ingestion of tree rather than peanuts were the major predictors of severe upper airway obstruction. The observation that tree nut allergy causes more severe anaphylaxis than peanut allergy has previously been reported,<sup>18,19</sup> although the specific link with pharyngeal edema has not. One possible reason

why both severe allergic rhinitis and tree nut allergy both predispose the pharyngeal edema is the cross-reactivity between certain tree pollen and tree nut allergens (eg, profilins).<sup>20,21</sup> Additional work is required to investigate these associations further.

Having recently had to treat a patient with a known peanut allergy who had previously only had symptoms of mild urticaria, but who after being prescribed enalapril and eating take-out food possibly contaminated with nuts developed life-threatening angioedema, another focus of this study was the possible relevance of enzymes involved in the catabolism of bradykinin in predicting this complication. Surges in bradykinin can induce life-threatening pharyngeal edema, for example in patients with hereditary angioedema,<sup>22</sup> but the relevance of this inflammatory nonapeptide

to food induced angioedema is unknown. Enalapril inhibits ACE, an enzyme involved in the breakdown of bradykinin. ACE is normally responsible for 70% to 90% of bradykinin catabolism, whereas APP is less important, accounting for only 10% to 30%.<sup>23</sup> Of patients taking ACE inhibitors, 0.1% to 0.7% develop angioedema,<sup>24</sup> and this is more common in patients with lower levels of APP.<sup>25</sup> We hypothesized that patients with nut allergy with the lowest ACE and/or APP activity would be most at risk of developing severe pharyngeal edema. In keeping with our hypothesis, this study showed that serum ACE levels were significantly lower in patients who developed severe pharyngeal edema than those with no pharyngeal symptoms, and patients with serum ACE concentrations in the lowest quartile had a relative risk of severe pharyngeal edema nearly 10 times that of patients in the rest of the cohort. This association was independent of age and sex. Other life-threatening allergic symptoms, such as severe bronchospasm and loss of consciousness, as well as less serious symptoms of urticaria were not associated with lower ACE levels. Serum APP activity, the function of which is generally overshadowed by ACE, did not predict the severity of upper airway obstruction.<sup>26</sup>

Serum ACE concentrations are known to fluctuate little in an individual throughout adult life, although there is some variation in childhood.<sup>27</sup> A one-off measurement of serum ACE levels is therefore likely to accurately reflect the usual ACE activity of that individual. However, activity does vary significantly between individuals because of an insertion/deletion polymorphism within the ACE gene.<sup>28</sup> Likewise, variation in APP levels between individuals is also known to be genetically determined.<sup>29</sup> Further studies examining the correlation between ACE polymorphisms and life-threatening pharyngeal edema induced by nuts may provide clues to the genetic basis for the patient variability in this symptom.

Our finding of an association between lower ACE levels and severe pharyngeal edema obviously needs confirmation in other large independent studies, but if confirmed may also have important implications for the treatment of patients with this life-threatening allergic symptom. It is known from the treatment of patients with hereditary angioedema that bradykinin-induced upper airway obstruction does not respond to epinephrine and corticosteroids and requires alternative therapies.<sup>30,31</sup> Rapid referral to the nearest emergency department for assessment and management of potential life-threatening upper airway obstruction is obviously important in any patient with anaphylaxis, particularly because in a significant proportion of patients (62% in this cohort), the first reaction to nuts was severe, and intramuscular epinephrine devices would not have been available. In the future, administration of specific bradykinin antagonists may also find a place as an adjunct to epinephrine in its management.

In terms of the predictive value of standard laboratory parameters usually measured in patients with nut allergy, we found no correlation between the severity of allergic reactions and the size of the allergen-specific SPT wheal, as previously documented by previous researchers.<sup>32</sup> In patients with peanut but not tree nut allergy, higher total and antigen-specific serum IgE levels were associated with more severe bronchospasm, although not with other allergic symptoms. Thus, our findings are in keeping with previous studies concluding that although standard allergy tests are useful in the diagnosis of peanut and tree nut allergy, they do not predict the severity of clinical reactions.

Allergic reactions to foods induce anxiety in a number of patients. We found that panic was most common in adults,

particularly women, and it was also independently associated with severe (but not mild) symptoms of upper airway obstruction and bronchospasm, although not circulatory insufficiency, peripheral edema, and urticaria. Our results therefore suggest that panic may be a psychological indicator of life-threatening allergic reactions (when it is not associated with obtundation of consciousness) signaling which patients may need urgent medical attention.

In conclusion, our study of patients referred to a single specialist allergy center provides evidence linking the severity of allergic reactions to peanuts and tree nuts with the severity of atopic disease, age, and serum ACE concentration. In so doing, it should help provide the clinician with a firmer basis for identifying patients at increased risk of nut-induced anaphylaxis.

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**Clinical implications: Clinical and laboratory parameters that best predict the likelihood of severe allergic reactions to peanuts and tree nuts are defined, suggesting how these reactions might be prevented and treated.**

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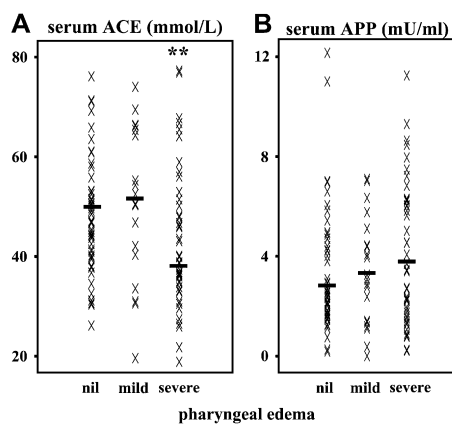


**FIG E1.** Serum ACE (**A**) and serum APP (**B**) concentration in patients with a history of no pharyngeal edema, mild pharyngeal edema, or severe pharyngeal edema after ingestion of peanuts and tree nuts. *Thick bar* represents median. \*\*Two-tailed  $P = .01$  using Kruskal-Wallis H test.

**TABLE E1.** Correlation between severity of various clinical symptoms after ingestion of peanuts and tree nuts

|                       | Bronchospasm |          |         | Reduced consciousness |         |        | Urticaria |          |          | Angioedema |          |         |
|-----------------------|--------------|----------|---------|-----------------------|---------|--------|-----------|----------|----------|------------|----------|---------|
|                       | Nil          | Mild     | Severe  | Nil                   | Mild    | Severe | Nil       | Mild     | Severe   | Nil        | Mild     | Severe  |
| Pharyngeal edema      |              |          |         |                       |         |        |           |          |          |            |          |         |
| Nil                   | 437 (70)     | 122 (20) | 64 (10) | 572 (92)              | 39 (6)  | 11 (2) | 243 (39)  | 193 (31) | 185 (30) | 233 (37)   | 355 (57) | 35 (6)  |
| Mild                  | 97 (53)      | 56 (30)  | 31 (17) | 156 (85)              | 27 (15) | 0 (0)  | 74 (40)   | 46 (25)  | 64 (35)  | 38 (21)    | 131 (71) | 15 (8)  |
| Severe                | 149 (53)     | 66 (23)  | 69 (24) | 205 (72)              | 57 (20) | 22 (8) | 126 (44)  | 51 (18)  | 107 (38) | 67 (24)    | 180 (63) | 37 (13) |
| Bronchospasm          |              |          |         |                       |         |        |           |          |          |            |          |         |
| Nil                   |              |          |         | 620 (90)              | 52 (8)  | 12 (2) | 290 (43)  | 198 (29) | 194 (28) | 248 (36)   | 397 (58) | 40 (6)  |
| Mild                  |              |          |         | 209 (86)              | 28 (12) | 6 (2)  | 86 (35)   | 72 (30)  | 86 (35)  | 59 (24)    | 164 (67) | 21 (9)  |
| Severe                |              |          |         | 105 (64)              | 44 (27) | 15 (9) | 67 (41)   | 21 (13)  | 76 (46)  | 31 (19)    | 107 (65) | 26 (16) |
| Reduced consciousness |              |          |         |                       |         |        |           |          |          |            |          |         |
| Nil                   |              |          |         |                       |         |        | 389 (42)  | 265 (28) | 277 (30) | 305 (33)   | 571 (61) | 58 (6)  |
| Mild                  |              |          |         |                       |         |        | 47 (38)   | 18 (14)  | 59 (48)  | 27 (22)    | 77 (62)  | 20 (16) |
| Severe                |              |          |         |                       |         |        | 6 (18)    | 8 (24)   | 19 (58)  | 6 (18)     | 18 (54)  | 9 (27)  |

Results are displayed as number (percentage). All correlations between severity scores are significant at  $P < .001$  using  $\chi^2$  statistics.