Clinical Features of Acute Allergic Reactions to Peanut and Tree Nuts in Children

Scott H. Sicherer, MD*; A. Wesley Burks, MD‡; and Hugh A. Sampson, MD*

ABSTRACT. Background. Peanut (PN) and tree nut (TN) allergies are potentially life-threatening, rarely outgrown, and appear to be increasing in prevalence. However, there is relatively little reported about the clinical features of acute reactions to these foods and their potential association.

Objective. To describe the clinical features of acute reactions during initial and subsequent accidental ingestions of PN and TN among children with a history of at least one acute allergic reaction to these foods.

Design. Questionnaire survey, examination, and serologic testing for specific IgE antibody of patients with convincing histories of acute reactions (at least one organ system involved within 60 minutes of ingestion) to PN or TN.

Results. A total of 122 patients (63% males; median age, 8 years at time of study) had acute reactions; 68 had reactions only to PN, 20 only to TN, and 34 to both PN and TN. Of those reacting to TN, 34 had reactions to one, 12 to two, and 8 to three or more different TN, the most common being walnut, almond, and pecan. Initial reactions usually occurred at home (median age, 24 months for PN and 62 months for TN) and were considered to result from a first exposure in most cases. Eighty-nine percent of the reactions involved the skin (urticaria, angioedema), 52% the respiratory tract (wheezing, throat tightness, repetitive coughing, dyspnea), and 32% the gastrointestinal tract (vomiting, diarrhea). Two organ systems were affected in 31% of initial reactions, and all three in 21% of reactions. Thirty-eight of 190 first reactions to PN or TN were treated with epinephrine. Accidental ingestions occurred commonly, but the extent and clinical relevance of acute reactions to these foods are potentially life-threatening, rarely outgrown, and appear to be increasing in prevalence. However, there is relatively little reported about the clinical features of acute reactions to these foods and their potential association.

Conclusions. Acute allergic reactions to PN occur early in life. PN and TN allergic reactions coexist in one third of PN-allergic patients, frequently occur on first known exposure, and may be life-threatening, requiring emergency treatment. Accidental ingestions are common, often occur outside of the home, and often require emergency treatment. Consequently, early diagnosis followed by education on avoidance and treatment measures (including self-administered epinephrine) is imperative.

ABBREVIATIONS. PN, peanut; TN, tree nut; GI, gastrointestinal; CAP System FEIA, a quantitative antibody fluoroscein-enzyme immunoassay; RAST, radioallergosorbent test.

Peanut (PN) and tree nuts (TN) are particularly important allergenic foods, but there is a paucity of reports about the clinical features of acute reactions to these foods. Unlike allergy to foods such as milk, egg, soy, and wheat, allergic sensitivities to PN and TN are rarely outgrown. In addition, allergic reactions to PN and TN appear to be more severe, and these allergens are most frequently associated with fatal reactions. The common consumption of PN among young children and the apparent increasing prevalence of allergic reactions to PN make additional research in this area vital. The sensitization of patients to both PN (a legume) and to TN has been commonly observed, but the extent and clinical relevance of this co-sensitization remain uncertain.

We undertook the present study to better characterize the nature of acute allergic reactions to PN and TN in children. A detailed history was obtained with the aid of a questionnaire, and specific IgE antibody levels were determined on pediatric patients presenting with a history of at least one acute reaction to PN and/or TN.

SUBJECTS AND METHODS

From December 1995 to May 1997, a detailed clinical history was obtained with the aid of a structured questionnaire from children evaluated in the Pediatric Allergy Clinic at Johns Hopkins Hospital, who had experienced at least one acute reaction to PN or TN. Reactions were considered to be convincing if ingestion of the suspected food resulted in a reaction involving one or more symptoms in one or more of the following organ systems (skin—lives, edema; respiratory—wheezing, throat tightness, repetitive coughing, shortness of breath; or gastrointestinal (GI) tract—vomiting, diarrhea) within 60 minutes of exposure. Histories generally were not confirmed by oral food challenges.

Because co-sensitization to PN and TN is frequently reported, sera were analyzed for specific IgE antibody levels to PN, a panel
of TN, and sesame seed (known to have cross-reacting proteins with hazel nut) with the CAP System quantitative antibody fluoroscein-enzyme immunoassay (FEIA) (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden). Serum samples were not obtained from 11 patients for reasons such as technical difficulty and parental preference. The lower limit of the assay is \(<0.35\) kU/L and the upper limit for undiluted serum is \(>100\) kU/L. For statistical analysis, values below detection were arbitrarily assigned a value of 0.34 kU/L, and those \(>100\) kU/L, a value of 101 kU/L. Statistical comparisons were performed with the Mann–Whitney U test and the Spearman correlation coefficient (\(r_s\)).

**RESULTS**

**Subjects**

The characteristics of the 102 patients experiencing an acute reaction to PN and the 20 experiencing acute reactions to at least one TN (but not to PN) are shown in Table 1. Of the 122 patients, there were 78 males (63%) and the median age at the time of evaluation was 8 years. There were 110 Caucasians, 8 African-Americans, and 4 Asian-Americans. The group was highly atopic and food-allergic, reflecting our tertiary referral population. Seventy-four percent had asthma, and 75% had atopic dermatitis. Eighty-one of the patients had a history of allergy to foods other than PN or TN; the majority of these food allergies were confirmed by convincing histories with supporting positive allergy skin prick tests, food-specific serum IgE antibody levels, and/or oral food challenges. The most common foods were egg (70 patients), milk (45), shellfish (18), fish (17), soy (14), and wheat (12). All but 9 patients had injectable epinephrine available for use in case of an accidental ingestion. Of these 9, 3 had not been prescribed the medication before referral, and the remainder forgot to renew prescriptions.

**Types of Nuts Responsible for Reactions**

Of the 102 patients with acute reactions to PN, 34% experienced reactions to at least one TN. The TN responsible for acute allergic reactions among 54 patients are shown in Fig 1. Among the patients with reactions to TN, 34 (63%) experienced a reaction to only one type, 12 (22%) to two types, and 8 (15%) had reactions to three or more types. Walnut, almond, pecan, and cashew were the most common TN responsible for reactions.

**First Allergic Reactions to PN**

Table 2 lists the characteristics of first reactions to PN. Seventy-two percent experienced a reaction with their first known exposure to PN (median age, 24 months; range 6 to 108 months). The median time to onset of symptoms was 3 minutes, with a range of <1 minute to 45 minutes, with 95% of patients experiencing symptoms within 20 minutes. Whereas half of the patients experienced isolated skin symptoms, very few (4 patients) experienced isolated GI or respiratory symptoms. None of the patients reported cardiovascular compromise, loss of consciousness, or decreased blood pressure.

Medications used for treatment included antihistamines (73%), epinephrine (19%), corticosteroids (13%), \(\beta\)-agonists (13%), and intravenous fluids (2%). Twenty-two patients were not given any medication at the time of their first reaction. Most patients were treated at home (51), whereas the remaining were treated in an emergency room (21), a doctor’s office (11), in school (3), at a relatives home, or in a car (1 each). Eight patients were treated first at home, and then treatment was continued in an emergency room or physician’s office.

**First Allergic Reactions to TN**

The characteristics of first acute allergic reactions to TN are summarized in Table 2; 88 episodes occurred in 54 patients. Although most of the characteristics were similar to those noted for PN, the median age of exposure (22 versus 54 months) and first reactions (24 versus 62 months) were significantly greater (\(P < .001\)) in patients reacting to TN. Treatments for these first episodes of allergic reactions to TN included antihistamines (70 patients), epinephrine (19), corticosteroids (12), \(\beta\)-agonists (14), intravenous fluids (4), and intubation (1). The location of the treatment for the reaction was reported in 65 cases: home (36), emergency room/hospital (17), doctors office (3), school (4), and other places including homes of relatives or friends (5).

**Accidental Ingestions**

Over a median period of 5.4 years from the time of the initial reaction, 55% of PN-allergic patients experienced reactions to accidental ingestions of PN, with an average of two accidents per patient among those reacting (range, one to five episodes). The median age at the time of a first accidental ingestion was 4 years. Accidental ingestions occurred most commonly in school (29), home (22), and restaurants (8). The symptoms were similar to those of the first reaction: skin only, 44%; respiratory only, 10%; GI only, 3%; skin with respiratory, 18%; skin with GI, 8%; GI with respiratory, 2%; all three systems, 15%. One patient experienced loss of consciousness. Treat-
ments were described in 84 instances and included epinephrine (16), antihistamines (72), steroids (9), β-agonists (17), and cimetidine and intravenous fluids (1).

There were fewer accidental ingestions to TN. Over a median period of 5.5 years from the initial reaction, 16 (30%) of the 54 patients experienced 21 accidental ingestions. The median age at the time of the first accident was 9.6 years. Epinephrine was required in eight cases.

Exposure History Among Patients With Acute Reactions to PN and TN

The majority of those with acute reactions to PN denied the ingestion of any particular TN (ranging from 57% who denied ever eating almond to 85% who denied ever eating Brazil nut). The majority of patients were told to avoid all TN by the investigators or previous physicians. Many of the remaining patients did not have the occasion to eat TN, were too young to be given TN, or were unsure of their exposure history.

PN was almost universally consumed by lactating mothers, and 93% of the mothers consumed at least one TN while breastfeeding. Mothers were asked which foods they consumed and which they specifically avoided during lactation. Although many mothers did not recall ingesting any particular TN, fewer than six mothers strictly avoided PN or any specific TN during lactation.

Results of Antigen-specific IgE Antibody Testing to PN and TN

In 111 patients in whom serum was obtained (91 of the 102 patients with acute allergic reactions to PN, with or without TN allergy, and all 20 patients with TN reactions), specific IgE antibody to PN, walnut, hazel nut, Brazil nut, almond, pecan, pistachio, pine nut, and sesame was determined. Table 3 shows the results of the CAP-System FEIA for the four foods responsible for acute allergic reactions in 10 or more subjects (analysis was not performed for the remainder of the nuts because too few subjects reported acute reactions). Patients reporting reactions to PN,
walnut, and pecan had significantly greater values of specific IgE antibodies toward the respective food than those ingesting the food without reactions. A total of 8 patients reported reactions to PN or TN, but had undetectable specific IgE antibody levels (<0.35 kU/L) as follows: PN (4/91 reactions), walnut (4/25), almond (3/11), pecan (2/11), pistachio (1/7), and Brazil nut (1/4). Among patients who believed that they never ingested a particular TN (>60% of patients for each nut), the majority had levels of specific IgE antibodies >0.34 kU/L, with median values as follows: walnut, 1.2; hazel nut, 2.7; Brazil nut, 2.2; almond, 3.6; pecan, 1.7; pistachio, 1.9; and pine nut, 0.4. The range of levels of specific IgE antibody for each food was from undetectable (<0.35 kU/L) to >100 kU/L.

Correlation coefficients of specific IgE antibodies for all 111 patients are shown in Table 4. In considering the group as a whole, specific IgE levels of all TN and sesame seed were highly correlated, whereas PN levels were not as highly correlated with walnut, pecan, or pistachio. The same analysis was performed on four subgroups: 1) 91 patients with acute reactions to PN, with or without an acute reaction to a TN, 2) 31 patients with acute reactions to PN and at least one TN, 3) 60 patients with reactions to PN but not to any TN, and 4) 20 patients with reactions to only TN. A similar pattern of correlation between the TN IgE antibody levels was noted in all subgroup analyses (data not shown). However, in the group of 20 patients with TN reactions alone, PN-specific IgE levels were more highly correlated with hazel nut ($r_s = 0.91; P \leq .0001$), almond ($r_s = 0.83; P \leq .0001$), sesame ($r_s = 0.83; P \leq .0001$), pine nut ($r_s = 0.74; P = .0002$), walnut ($r_s = 0.66; P = .001$), and pecan ($r_s = 0.48; P = .03$).

### DISCUSSION

Immediate hypersensitivity reactions to PN (a legume) and TN are a potential cause of anaphylaxis and death.6–8,13 The exact prevalence of allergic sensitization to PN and TN is not known, although estimates of PN sensitization among atopic patients has been reported to be ~10%.14 A recent study by Tariq and colleagues using skin prick testing found a sensitization rate of 1.2% and a reaction rate of 0.7% to PN or TN in a birth cohort of 1218 children on the Isle of Wight, UK, followed to age 4. Allergy to PN and TN appears to be rarely outgrown and remains an important cause of food-allergic reactions in adults.1,2,4,6,15 The results of our study highlight a number of features of acute reactions to PN and TN in children and raises questions that require additional study.

The diagnosis of PN and TN allergy in our study patients was based on a convincing history of an acute reaction to an isolated ingestion of the food. In 5 of 102 instances of acute reactions to PN and in 12 of 88 reactions to TN (among 9 patients in total), there was an undetectable level of specific IgE antibody levels to the food in question. This could represent a loss of sensitivity in some patients15 (although none described the ability to ingest the food without symptoms after having had the initial reaction), a misidentification of the responsible allergen, or lack of sensitivity of the test.

One striking feature of first reactions to PN was the young age at the time of the initial reaction (median, 24 months; range, 6 to 108 months). Similarly, studies in the United Kingdom showed that first reactions occurred by 24 months in approximately half of 60 patients who developed PN aller-

### TABLE 3. PN- and TN-Specific IgE Levels (kUA/L) in Patients With or Without Acute Reactions

<table>
<thead>
<tr>
<th></th>
<th>Reactors</th>
<th>Nonreactive</th>
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<tr>
<td></td>
<td>Mean</td>
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</tr>
<tr>
<td>PN</td>
<td>51.7</td>
<td>46.3</td>
<td>91</td>
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<tr>
<td>Walnut</td>
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<td>Almond</td>
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<tr>
<td>Pecan</td>
<td>18.3</td>
<td>1.9</td>
<td>11</td>
</tr>
</tbody>
</table>

* Comparing those with a history of a reaction with those who have eaten the food without a reaction.

### TABLE 4. Correlation ($r_s$) Between the Serum Levels of PN-, Sesame-, and TN-specific IgE in 111 Patients and in Subgroups With PN or Only TN Reactions

<table>
<thead>
<tr>
<th></th>
<th>PN</th>
<th>Walnut</th>
<th>Hazel</th>
<th>Brazil</th>
<th>Almond</th>
<th>Pecan</th>
<th>Pistachio</th>
<th>Pine Nut</th>
<th>Sesame</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
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<td></td>
<td>0.26 (P = .001)</td>
<td>0.60*</td>
<td>0.56*</td>
<td>0.58*</td>
<td>0.23 (P = .02)</td>
<td>0.26 (P = .005)</td>
<td>0.37*</td>
<td>0.50*</td>
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<tr>
<td>Walnut</td>
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<td>0.53*</td>
<td>0.63*</td>
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</tr>
<tr>
<td>Hazel</td>
<td>0.73*</td>
<td>0.73*</td>
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<td>0.64*</td>
<td>0.83*</td>
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<tr>
<td>Brazil nut</td>
<td>0.61*</td>
<td>0.73*</td>
<td>0.54*</td>
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<td>0.59*</td>
<td>0.83*</td>
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<tr>
<td>Almond</td>
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<tr>
<td>Pistachio</td>
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<td>0.54*</td>
<td></td>
<td>0.63*</td>
<td>0.59*</td>
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<tr>
<td>Pine nut</td>
<td>0.60*</td>
<td>0.60*</td>
<td>0.54*</td>
<td>0.55*</td>
<td>0.63*</td>
<td>0.59*</td>
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* Correlation is weak if $r_s \leq 0.4$, moderate if $r_s = 0.4–0.7$, and strong if $r_s \geq 0.7$.

* P < .0001.
The high rate of accidental ingestions seen in this study, particularly for PN, is of clinical concern. Bock and Atkins\(^2\) found that among 32 patients with PN allergy followed for up to 14 years, 75% experienced an accidental ingestion. In the present study, accidental ingestions to TN occurred in 55% of the patients over a median period of 5.4 years, with an average of two accidents per patient in those experiencing accidents. In contrast to the initial reactions that occurred primarily at home, a larger proportion of the accidental ingestions occurred in school. This fact underscores the importance of having medications and an emergency plan in place for the rapid administration of emergency medication, particularly epinephrine, when children with severe PN and TN allergies are outside of the home.\(^7\)

The modes of accidental exposure to PN included hidden ingredients in processed foods, cross-contamination, sharing food with friends, and skin contact with peanut butter in school classroom projects. Restaurants also were particularly risky, especially Asian restaurants that may use PN in many foods, increasing the likelihood of cross-contamination. There were relatively fewer accidental ingestions of TN compared with PN, probably reflecting the more ubiquitous presence of PN in the food supply.

The relationship of PN and TN allergy has been addressed by a number of investigators,\(^2,5,9,10,16\) and it remains unclear whether patients with PN allergy are at an increased risk for TN allergy. In surveys in the United Kingdom, \(\sim 50\%\) of PN-allergic patients also reported reacting to at least one TN.\(^6,9,10\) Of the 102 PN-allergic patients in this report, 34% reported having a reaction to a TN. This percentage of nut reactors may be lower than that reported in the United Kingdom because our patients are younger and have been advised to avoid TN. Among those who reported reactions to TN, 12 (22%) reported having reactions to more than one TN, a finding that has been reported previously\(^6\) and confirmed in double-blind, placebo-controlled food challenges.\(^2\)

Evaluation of nut-specific IgE showed that a significant proportion of PN-allergic children are sensitized to TN. Whether these sensitivities reflect a response to cross-reacting proteins (which may or may not be clinically relevant) or a general increase in propensity to form specific IgE antibody to allergenic proteins is unclear. The generally high correlation of specific IgE antibody levels among the foods seen in our patients could support either hypothesis. For example, 57% of our study population also were sensitive to egg. It is known that PN-allergic patients have an increased rate of IgE sensitivity to egg,\(^1\) which would support the hypothesis that TN sensitivity is not peculiar to PN-allergic patients but merely reflects a greater likelihood to form IgE antibodies to allergenic proteins. Alternatively, cross-reacting proteins may be playing a role. For example, hazel nut and sesame showed the highest cross-reactivity in our study, a correlation that was shown previously.\(^11\) Using RAST inhibition, Gillespie and colleagues\(^16\) found no cross-reactivity between PN and Brazil nut, but the RAST for pecan was inhibited by PN, Brazil nut, and walnut, whereas the RAST for PN was inhibited by pecan. Additional studies correlating RAST inhibition results and oral challenges will be needed to clarify these issues.

For PN, walnut, and pecan, we found that levels of specific IgE antibody levels were higher in subjects who experienced an acute reaction to the particular food than in those who eat the food with impunity. However, there was a great overlap in values among those with and without reactions. For example, many patients who ate almond had elevated almond-specific IgE levels. It is unknown whether this represents exposure with resulting clinically irrelevant, elevated IgE antibody or an immunologic response to cross-reactive proteins. As with all IgE antibody tests for food allergy (skin prick tests or RAST), positive results do not always indicate clinical reactivity\(^3\) (poor sensitivity and specificity), whereas negative results have a high negative predictive value. A recent study in children with food allergy and atopic dermatitis showed that a PN-specific IgE level \(> 15 \text{ kU} /\text{L}\) had a 95% positive predictive value for experiencing a clinical reaction on ingestion of PN, whereas an undetectable level had an 85% negative predictive value for a reaction.\(^12\) Interestingly, that study did not show any correlation between specific-IgE level and severity of reaction.

There are conflicting views on whether patients with PN allergy should avoid TN.\(^2\) As reported here and elsewhere,\(^2\) many TN-allergic patients do not react to PN ingestion and visa versa. Although it may be overly restrictive, we and others\(^2\) advise complete avoidance of TN by PN-allergic children, except for any particular TN that was tolerated previously. Reasons for this recommendation include the concern that TN sensitivity appears to be severe and lifelong, that there is a potential for cross-contamination of TN products with PN\(^8\) and, finally, that it often is difficult to identify specific nuts in various processed foods.\(^15-19\)

A large proportion of the patients report reactions to PN and TN on what was perceived to be their first exposure, a finding reported previously.\(^5,9,20\) Several possibilities may explain this phenomenon: recall bias, inadvertent or unknown exposure, sensitization...
by cross-reacting allergens, in utero exposure, and/or exposure through breast milk. The possibility of sensitization through breast milk is intriguing. In a population study on the Isle of Wight, there was no association between the duration of breastfeeding or history of maternal ingestion of nuts and sensitization as measured by skin prick tests and RAST. However, a survey of the families of 622 PN-allergic probands in the United Kingdom noted an increased prevalence of PN allergy in succeeding generations. It was also noted that mothers of younger probands (younger than age 6) were more likely to have consumed PN at least weekly while pregnant or breastfeeding than were mothers of older probands, suggesting to those workers that sensitization had occurred in utero or during lactation. The present study was not designed to investigate specifically routes or risks of sensitization, but several interesting points deserve comment. First, virtually all of the lactating mothers consumed PN and at least one TN. Second, a large proportion (from 50% to 82%) of patients who did not report ever ingesting a particular nut had a detectable level of antibody to that nut, emphasizing the possibility that covert sensitization occurs, perhaps in part through sensitization from maternal intake. Additional research is needed on the relationship of PN and TN exposure in utero and during lactation to allergic sensitization to these antigens.

In this group of atopic patients referred for evaluation of acute reactions to PN and TN, significant reactions occurred early in life, on what was often perceived to be the first exposure to the food, and frequently required emergency treatment. Accidental ingestions were common, sometimes life-threatening, required emergency treatment, and often occurred in locations outside of the home. Symptoms did not always involve the skin, although it was the organ system affected most often. Thirty-seven percent of PN-allergic patients also had acute reactions to at least one TN. Attempts to treat PN allergy with immunotherapy have had limited success with prohibitive side effects, and the only current treatment for these allergies is strict avoidance of the offending food and prompt recognition and treatment of reactions. These findings emphasize the need for education of families, patients, caregivers, and health care workers in PN and TN avoidance and treatment of reactions.

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