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The diagnosis of Brazil nut allergy using history, skin prick tests, serum-specific immunoglobulin E and food challenges

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Summary

Background Allergy to Brazil nut is a relatively common nut allergy and can be fatal. However, the evidence is lacking regarding the best approach to its diagnosis.

Objective We sought to determine the relative merits of history, skin prick testing, measurement of serum-specific IgE and challenge in the diagnosis of Brazil nut allergy.

Methods Fifty-six children and adults with a history of an allergic reaction to Brazil nut or evidence of sensitization were investigated by questionnaire ($n = 56$), skin prick tests (SPTs) ($n = 53$), measurement of serum-specific IgE to Brazil nut ($n = 54$) and double-blind, placebo-controlled labial, and if necessary oral, challenges ($n = 19$).

Results Brazil nut allergy occurred in highly atopic individuals of any age with a strong family history of atopy. In 24 of 56 (43%), the history of an immediate reaction was sufficient to make a diagnosis with confidence and an oral challenge was considered unsafe. Of the 19 subjects undertaking the 'gold standard' test of a double-blind, placebo-controlled, food challenge, all six subjects with a SPT of at least 6 mm had a positive challenge and all three subjects with a SPT of 0 mm had a negative challenge. In the remaining 10 (53%) subjects, where SPT was between 1 and 5 mm and serum-specific IgE was less than 3.5 kU/L, an oral challenge was performed resulting in three positive and seven negative challenges.

Conclusion A combination of history, SPT and serum-specific IgE was adequate in achieving a diagnosis in the majority (77%) patients with suspected Brazil nut allergy. However, a doubtful history with SPT between 1 and 5 mm, or a serum-specific IgE less than 3.5 kU/L may require an oral challenge to help determine the risk of a Brazil nut allergic reaction.

Keywords allergy, Brazil nut, labial challenge, oral challenge, skin prick test, specific IgE

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Introduction

Allergy to the fruits of the Brazil nut tree (*Bertholletia excelsa*) has been identified as the most common tree nut allergy in one British paper on consecutive cases of peanut and nut allergy [1] and another on anaphylaxis [2]. The diagnosis of Brazil nut allergy is usually made on the basis of history and examination at the time of a reaction, with confirmation by investigative procedures such as skin prick test (SPT), measurement of serum-specific IgE and challenge procedures. Suspected food allergy is often difficult to diagnose or refute because of the lack of precision in the available diagnostic methodology. Unless the history clearly suggests an immediate and reproducible reaction, the same is true for Brazil nut allergy. Interpretation of SPT may be difficult and the presence of serum-specific IgE alone does not necessarily prove clin-

ical reactivity. The double-blind, placebo-controlled, food challenge (DBPCFC) is considered to be the 'gold standard' investigation but it is time consuming, costly and there is a definite, although small, risk of a serious anaphylactic reaction. The use of DBPCFC should, therefore, be restricted to those cases where the diagnosis could not be made by other means. In clinical practice, it would be helpful if the diagnosis can be confidently made or refuted by history, SPTs and blood tests alone. Although these tests are commonly used in the management of Brazil nut allergy, the sensitivity, specificity and the diagnostic accuracy of these tests remain uncertain.

Methods

Subjects with presumed or suspected allergy to Brazil nut were invited to participate in this prospective study. All

had a history of an allergic reaction to Brazil nut, or evidence of sensitization (positive SPT or serum-specific IgE) to Brazil nut with no known reaction. These subjects were recruited from the allergy clinic or responded to local advertisement from June 1998 to March 2000. Ethical approval was obtained from the Isle of Wight Health Authority Local Research Ethics Committee.

Participants completed a questionnaire that included questions on their history of reactions to Brazil nuts, symptoms experienced and a personal and family atopic history. SPT were performed to aeroallergens, nuts and egg (ALK Soluprick, Hørsholm, Denmark or Bayer Corporation, Newbury, UK). The mean of two diameters from the resultant weal was recorded. For consistency, one experienced nurse performed all SPT. Reproducibility was assessed in 35 cases, where SPT were performed in duplicate using both arms. These duplicated SPT reaction sizes were compared using the Bland–Altman method [3] and the differences were found to be not significant, confirming reproducibility of the test. However, in the lower range, duplicate weals could be either side of the 3 mm cut off point (e.g. 1 and 3 mm) that is often used to determine a positive result [4–7]. As this cut off point is somewhat arbitrary, we have used a continuous range of values for assessment of Brazil nut sensitization and its usefulness as a discriminatory test.

Blood samples were taken and serum-specific IgE to Brazil nut was measured using the Pharmacia CAP system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Levels less than 0.35 kU/L were considered undetectable.

To avoid unnecessary risk, DBPCFC were not performed if there was a history of a recent immediate reaction to Brazil nut (defined for this study as within the last 5 years) or if the subject had ever had a serious, systemic or life-threatening reaction involving respiratory or cardiovascular symptoms and SPT or serum-specific IgE were positive. Therefore, the selection criteria for Brazil nut challenges to confirm allergy were as follows:

- when the history was unclear or last reaction was more than 5 years ago (regardless of SPT or serum-specific IgE);
- history was suggestive but negative test results (defined as undetectable serum-specific IgE or SPT less than 3 mm) contradicted their clinical history;
- positive SPT or serum-specific IgE, with no known previous reaction to Brazil nut.

Brazil nut allergy was considered to be confirmed in those with:

- a positive challenge;
- a history of a definite, recent (within 5 years) reaction or of a serious, systemic reaction at any time, supported by SPT of at least 3 mm or serum-specific IgE greater than 0.35 kU/L.

Appropriate safety precautions were taken during the challenge procedures.

A double-blind placebo-controlled labial challenge procedure was performed before the oral challenge in order to protect a strongly sensitive patient from exposure to higher doses of ingested allergen. The procedure was adapted from that used previously [8, 9] which was shown to have a sensitivity of 74–77%. Vital signs and a facial photograph were obtained before and during the labial challenge. With an eye mask and nose clip in place, either the cut surface of a shelled Brazil nut or a placebo (a smooth surfaced stone) was wiped across one side of the upper lip. Any reaction was allowed to subside before proceeding to the second stage using the other side of the lip. The labial challenge was considered positive if definite signs such as erythema, swelling or urticaria were observed. Subjective symptoms alone such as irritation or discomfort of the lip or in the mouth or throat were defined as inconclusive. If the labial challenge was negative or inconclusive the patient proceeded to a double-blind oral challenge.

Flapjack biscuits (cookies based on oats and syrup) were prepared either containing ground Brazil nut (equivalent to one Brazil nut or 0.53 g protein per biscuit) or no nut. Prior to this study these had been extensively tested on 25 non-allergic adults and children and were indistinguishable on grounds of appearance, taste or smell. One biscuit was ingested in a double-blind manner in gradually increasing quantities at intervals of 15 min starting with 1/32 of a biscuit. Vital signs of pulse, blood pressure and peak flow rate were monitored and the patient observed for evidence of an allergic reaction including rash, pruritus, angio-oedema, rhino-conjunctivitis, respiratory signs including cough and wheeze, gastrointestinal effects such as abdominal pain and vomiting and general demeanour. The challenge procedure was halted if a definite reaction was provoked. Symptoms were allowed to subside before proceeding with the second flapjack. If no reaction was seen to either challenge, the patient proceeded to an open challenge and ate at least one whole Brazil nut, so the total ingested during the challenge was two nuts equivalent to 1.06 g protein. One subject reported mild oral symptoms only during the nut phases of both the labial and oral challenge. The oral challenge was therefore repeated on two separate occasions. In total he correctly identified four placebo and four nut phases, so the challenge was classed as positive.

Results

Fifty-six patients were recruited (male:22). Ages ranged from 4 to 83 years (median 18 years, inter-quartile range 10–35 years). Three did not attend for skin prick testing, two children declined blood sampling. Fifteen had never

knowingly had a reaction to Brazil nut of whom 11 had never eaten them, three had previously eaten them but not reacted and one had had a reaction but could not be sure that Brazil nut had caused it. Thirteen did not undergo challenge despite not meeting the criteria to confirm Brazil nut allergy. Of these thirteen, eight declined, three agreed but did not attend two arranged appointments and in two oral challenges were contraindicated because of significant cardiovascular disease. Oral challenge was not required in 24 cases as 19 had a good history of a recent reaction and five had had a severe reaction, all of which were confirmed by tests. Nineteen undertook a challenge to complete the study protocol as shown in Fig. 1. Four labial challenges were positive and the 15 with negative or inconclusive labial challenges proceeded to oral challenge, of which five were positive and 10 were negative.

The questionnaire responses showed this group to be highly atopic and to have strong family histories of atopy in first-degree relatives as illustrated in Table 1. This notion is further strengthened by the fact that all except one of the cases had at least one positive SPT to an allergen other than Brazil nut (when using the definition of a positive SPT as at least 3 mm in mean diameter). Only 40% were sensitized to peanut, and the nut sensitivity most likely to be associated with Brazil nut was hazelnut (Fig. 2).

Skin prick reactions to Brazil nut were less than 3 mm in nine cases. Seven had previous records of a SPT of at least 3 mm or a positive serum-specific IgE to Brazil nut and two were included in the study solely on the grounds of a convincing history of reaction despite negative test results.

Questionnaire responses from the 41 cases that could recall reacting to Brazil nuts helped clarify the typical reaction and range of reactions. Thirty-one reported that they had reacted to tiny quantities of Brazil nut, such as a taste, a touch or the smell when nuts were cracked, whereas four had eaten less than one nut and only three had eaten more than one nut before a reaction occurred. Most reported that their reactions started immediately: 25 cases within 1 min, 10 between 1 and 5 min, four between 5 and 30 min and two cases between 30 min and 2 h. Although most reactions lasted less than 3 h some symptoms persisted for many hours.

The symptoms experienced during a reaction ranged from mild discomfort in the mouth in nearly all cases through to rare collapse (Table 2). Only two felt that exercise had influenced a reaction and three described a late phase reaction whereby their symptoms had started to improve and then deteriorated again.

A clear history of an allergic reaction within the last 5 years correlated well with SPT result as all had a weal of at least 3 mm apart from one of 2 mm. However, six of 23 (26%) with a recent history had undetectable serum-specific IgE. In those who reported a reaction more than 5 years ago ($n = 18$) there were two SPTs less than 3 mm and six with undetectable serum-specific IgE.

The correlation between size of the SPT weal and the level of serum-specific IgE to Brazil nut was only moderate (Spearman's rank correlation coefficient = 0.437) but significant at the 0.01 level (two-tailed).

Nineteen challenges were performed of which nine were positive and 10 were negative. Of the 13 cases who did not undergo challenge despite not meeting our criteria to

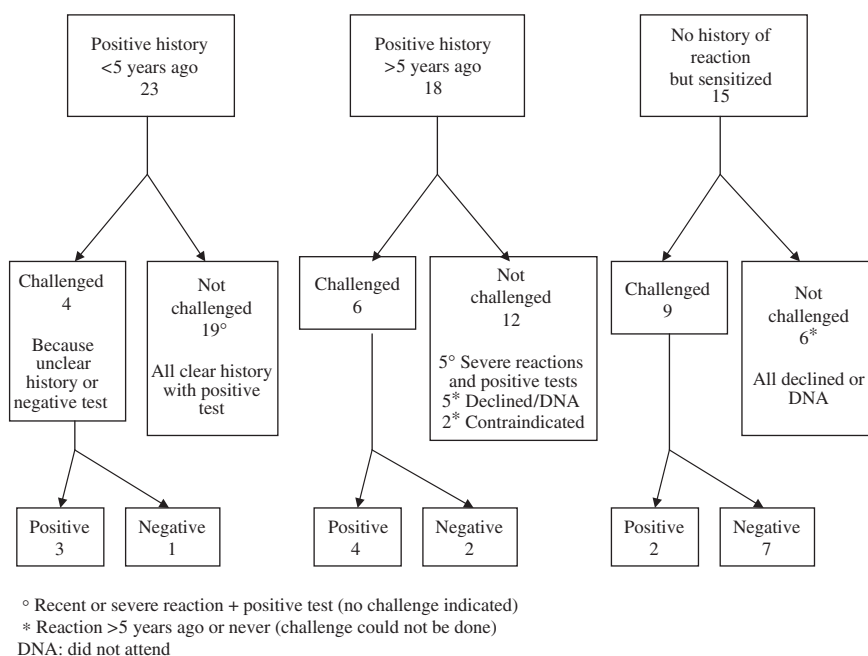


Fig. 1. Flow chart showing the study procedure for the 56 Brazil nut allergic or sensitized patients.

Table 1. Atopic history of 56 questionnaire respondents

	Number	Percentage (%)
Eczema	42	75
Asthma	40	71
Allergic rhinitis	49	88
Egg or milk allergy in infancy	27	48
Family history of atopy in first degree relative	52	93
Family history of nut allergy	4	7

confirm allergy, four had a good history of a reaction to Brazil nuts more than 5 years ago and still had positive SPT and/or serum-specific IgE. Although not confirmed by challenge these four are likely to have retained clinical reactivity to Brazil nuts. The results, summarized in Fig. 3, show that clinical reactivity was proven by positive challenge in two cases with an SPT weal less than 3 mm (although never when no weal at all is demonstrated), and in four cases with undetectable (class 0) serum-specific IgE. Negative challenges were found with a SPT up to 5 mm and serum-specific IgE up to 2.28 kU/L (class 2). In attempting to predict clinical reaction in this population, it is not possible to find one cut-off point for SPT or serum-specific IgE that gives a satisfactory sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) (Table 3). However, some useful conclusions can be drawn. A SPT with no measurable weal rules out the possibility of Brazil nut allergy and a SPT of at least 6 mm is confirmatory. Thus there is no need for challenge with these SPT reaction sizes. When the history is in doubt and SPT size is between 1 and 5 mm, oral challenge is indicated. Serum-specific IgE was less discriminatory, as there were positive challenges when serum-specific IgE was undetectable (class 0). Those with serum-specific IgE > 3.5 kU/L were all definitely allergic to Brazil nut (history of severe reaction or positive challenge), but all except one of these subjects also had a SPT reaction size of ≥ 6 mm (the other was 5 mm).

The importance of history was shown as the initial diagnosis of Brazil nut allergy had been made by 29 of

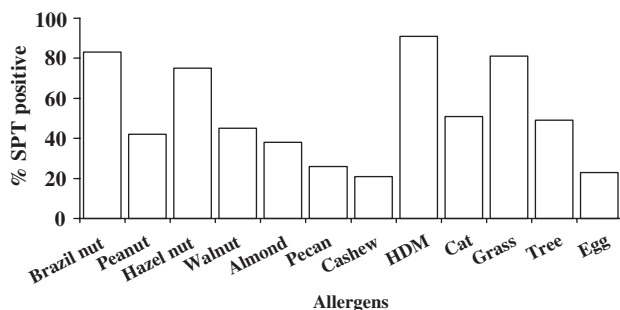


Fig. 2. Number of positive skin prick tests (SPTs) (≥ 3 mm) to various allergens performed in 53 cases.

Table 2. Symptoms experienced by 41 patients during reactions to Brazil nuts

Symptom	Number	Percentage (%)
Irritation/discomfort of mouth or lips	39	97
Swelling of lips or tongue	35	85
Throat tightening/difficulty in swallowing	33	80
Swelling/puffiness of face or eyelids	28	68
Skin rash	23	58
Increased heart rate	20	56
Shortness of breath	21	51
Sense of doom/fear	16	42
Nausea/abdominal pain/vomiting	17	41
Wheezing	16	40
Stridor	13	32
Collapse/unconsciousness	1	3

56 (52%) patients themselves following a reaction obviously caused by Brazil nuts. Of these, 25 were confirmed and only two had negative challenges. In the group of 15 patients who did not have a history of an allergic reaction to Brazil nut, each had a positive SPT and/or serum-specific IgE. Nine of these were challenged of which only two were positive, which emphasizes the importance of challenges when there is no clear history.

In summary, of 56 subjects with suspected Brazil Nut allergy, 13 declined to undergo challenge. Of 43 with complete data, a confident diagnosis could be made initially in 24 with a clear recent history plus SPT of at least 3 mm and serum-specific IgE greater than 0.35 kU/L.

Specific IgE (kU/L) [class]	>17.50 [4]					●●●	●+
	3.50–17.49 [3]				●	●	●●●●*
	0.70–3.49 [2]	●		●++	●●●●	●●	●●
	0.35–0.69 [1]	●	×+		●×		●●●●●
	<0.35 [0]	+	××+	●++	●●●×	●*	●●*
	IgE not analysed				●	+	
	SPT not done	0	0.1–2.9	3–5.9	6–10.9	11–20.9	21+
Skin Prick test weal size (mm)							

- Confirmed by challenge (9)
- Confirmed without challenge (recent or severe reaction + positive tests) (24)
- * No challenge, reaction >5 years ago, positive tests (4)
- × Negative challenge (10)
- + No challenge, reaction >5 years ago + negative tests, or no reaction (9)

Fig. 3. Comparison of skin prick test and serum-specific IgE with level of confirmation of Brazil nut allergy.

Table 3. Sensitivity, specificity, positive predictive value and negative predictive value of skin prick test (SPT) and serum specific IgE

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
SPT > 0 mm	1	0.3	0.82	1
SPT ≥ 3 mm	0.94	0.33	0.83	0.61
SPT ≥ 6 mm	0.77	1	1	0.59
IgE ≥ 0.35 (class 1)	0.84	0.55	0.88	0.47
IgE ≥ 0.7 (class 2)	0.66	0.7	0.88	0.39
IgE ≥ 3.5 (class 3)	0.38	1	1	0.33

Following oral challenges in the remaining 19 subjects with vague history, it became clear that a confident diagnosis could have been made in another nine, using SPT criteria alone (0 mm refuted the diagnosis and ≥ 6 mm confirmed it). Those 10 subjects with SPT between 1 and 5 mm required an oral challenge to clarify the diagnosis.

Discussion

In the field of allergy, history alone has often been used to make a diagnosis [6, 10] and patients will often make their own diagnosis [11]. Indeed, 52% of our patients first believed they were Brazil nut allergic following a reaction rather than from tests. Researchers too, may rely on history as most studies on oral challenges exclude a proportion of patients from the challenge procedure because of a convincing history of an immediate moderate or severe reaction after ingestion of only one possible allergen [7, 9, 12–14]. However, caution is needed as questionnaire-based diagnosis can give false positives [11] and so tests are often used to clarify the situation.

Our results suggest that Brazil nut allergy occurs in those with a strong family history of atopy and with a strong personal propensity to develop other allergies. Seventy percent were found to have asthma, which can influence the severity of an allergic reaction. Nearly all have sensitivities either to aeroallergens or to other food allergens with house dust mite, grass pollen and hazelnut being most common.

The typical allergic reaction to Brazil nut is similar to IgE-mediated reactions to peanuts and other foods in that it occurs immediately following minimal contact or ingestion [9, 15, 16]. Symptoms vary in different individuals and range from mild oral symptoms to life-threatening anaphylaxis. Respiratory effects such as laryngeal oedema are thought to be the main life threatening danger in nut allergies [1, 17, 18] and so it is of note that the feeling of throat tightening was reported by 80% of those suffering reactions to Brazil nuts. Most people suffered symptoms of peri-oral angio-oedema, while urticaria was common and lower respiratory symptoms such as wheezing and cardiovascular symptoms were less common.

The history may be unreliable because of a number of reasons including the length of time since the reaction, atypical symptoms, the timing of the symptoms or a mix of different foods being ingested. In clinical settings, tests confirming the history are often used to make a firm diagnosis [4]. Negative SPT and blood tests can lead to doubt over the diagnosis even in the presence of a history suggestive of a reaction to nuts [4]. One of our cases with a recent history of reaction to Brazil nut had a weal of only 2 mm (traditionally regarded as negative), although no SPT was completely negative with a recent history. However, five subjects had undetectable serum-specific IgE with a clear history or positive challenge, so SPT results and serum-specific IgE in particular, cannot alone be relied upon to make a firm diagnosis in all cases.

Positive results should also not be interpreted in isolation. In one study of nut allergy 9 of 16 children with positive serum-specific IgE had negative challenges [12]. We found negative Brazil nut challenges in people with a SPT up to 5 mm and serum-specific IgE up to 2.28 kU/L. From our data an attempt was made to identify test levels that could be useful clinically in diagnosing or refuting Brazil nut allergy. A SPT of 6 mm or a serum-specific IgE of 3.5 kU/L (class 3) would give a PPV of 100% (so confirming allergy) and a SPT of 0 mm would give a NPV of 100% (so refuting allergy). Similarly, in other food allergies attempts have been made to identify cut-off levels with suggestions of SPT of 6 mm [13] and 8 mm [19] to confirm peanut allergy and in atopic dermatitis a CAP serum-specific IgE to peanut of 15 kU/L gave a PPV of 95% [7].

It is common practice to designate a certain weal diameter (usually 3 mm) in SPTs as a positive result. However, there is crossover between groups and our duplicated tests were sometimes either side of this level. The precise measurement should always be assessed in conjunction with the history and if necessary other tests or a challenge should be performed to confirm the result.

We found levels of serum-specific IgE of < 0.35–2.28 kU/L for those with negative challenges and < 0.35–51.8 kU/L for confirmed cases of Brazil nut allergy. Pasterello et al. [20] looked at people with positive serum-specific IgE to Brazil nut who could be symptomatic (2.87–> 100 kU/L) or asymptomatic (0.8–3.12 kU/L). Only sera from the symptomatic patients recognized a 9 kDa allergen that corresponded to a 2S albumin, whereas sera from the asymptomatic cases recognized minor allergens in the range of 25–58 kDa. The 2S albumin was also characterized by Bartolome et al. [21] and it was this sulphur-rich protein transferred by Nordlee et al. [22] to soybean by transgenic engineering, which also transferred the allergenic potential. There is scope to improve the diagnostic properties of both skin test solutions and serum-specific IgE measuring kits for Brazil nut by more closely identifying the major allergens.

The so-called 'gold standard' test for food allergy is the DBPCFC. However, it is important to ensure that an adequate amount of the food has been administered, before the challenge can be considered negative [23]. False-negative results are rarely reported with this procedure [4, 12] although Burks reported a 7.9% recurrence rate for peanut allergy after diagnosis of resolution by DBPCFC [24]. In this study, a 14-year-old boy reacted to Brazil nuts only weeks after a negative challenge. He was challenged as, despite a SPT of 5 mm and serum-specific IgE of 0.63 kU/L, he had no history of reaction to Brazil nut having avoided all nuts since a reaction to peanuts when aged 1 year. The double-blind placebo-controlled challenge was negative and he ate a further four Brazil nuts in the open part of the challenge. In the weeks following the challenge he ate Brazil nuts in isolation on two occasions. The first time no reaction occurred after eating two Brazil nuts but on the second exposure he reacted with angio-oedema, vomiting and wheezing after eating four nuts. His symptoms settled after antihistamine therapy. It may be that he had been re-sensitized by the challenge having previously avoided Brazil nuts. Although, apparently a rare event, a negative challenge cannot therefore completely rule out a future reaction in someone with strongly positive tests.

Food challenges are used in clinical practice to exclude or confirm the diagnosis where there is any doubt from history, skin prick testing or blood testing. However, respiratory symptoms [23] or even haemodynamic changes [25] may be induced. It is important therefore that such challenges are only performed in centres with appropriate facilities and experienced staff. In addition, challenges are not always welcomed by patients. Eleven of our cases declined a challenge or did not attend having previously agreed to it. In another study only one of 34 children offered repeated challenge for peanut allergy agreed to it [5] and in children who were challenged to confirm resolution of peanut allergy, aversion and continued avoidance was common even after a negative challenge [13]. One benefit of challenges noted incidentally was in those who had never suffered an allergic reaction to nuts or who had been too young to remember the symptoms. Following their challenge experience they were more likely to recognize any future reaction early on, so enabling them to seek prompt treatment.

Conclusions

Brazil nut allergy tends to occur in highly atopic individuals of any age with a strong atopic family history. The results indicate that no one method of diagnosing Brazil nut allergy is totally reliable as even an oral challenge gave a misleading result in one patient. Features in the history that suggest Brazil nut allergy include an immediate reaction to a small quantity of Brazil nut involving

typical symptoms especially those of peri-oral angio-oedema. A good recent history can be confirmed by a positive SPT or serum-specific IgE. In the absence of a reliable recent history, a negative SPT or a weal diameter of 6 mm or greater is sufficient to refute or confirm allergy, respectively. Addition of serum-specific IgE result to SPT is not helpful. If SPT is not available, a serum-specific IgE of class 3 or more (> 3.5 kU/L) confirms clinical reactivity. These extreme values could be used as a basis to diagnose or refute the diagnosis of Brazil nut allergy without always resorting to oral challenge. Results between these levels may require an oral challenge to help determine the risk of a Brazil nut allergic reaction, although a negative challenge does not completely exclude all risk of future reaction.

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References

- 1 Ewan PW. Clinical study of peanut and tree nut allergy in 62 consecutive patients: new features and associations. *BMJ* 1996; 312:1074–8.
- 2 Pumphrey RSH, Stanworth SJ. The clinical spectrum of anaphylaxis in north-west England. *Clin Exp Allergy* 1996; 26: 1364–70.
- 3 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 307–10.
- 4 Baker H, Luyt D, Stern M. Open challenge to nuts in children. *Allergy* 1999; 54:79–80.
- 5 Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989; 83:900–4.
- 6 Hourihane J O'B, Dean TP, Warner JO. Peanut allergy in relation to hereditary, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996; 313:528–21.
- 7 Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; 100: 444–51.
- 8 Rance F, Dutau G. Labial food challenge in children with food allergy. *Pediatr Allergy Immunol* 1997; 8:41–4.
- 9 Moneret-Vautrin DA, Rance F, Kanny G *et al.* Food allergy to peanuts in France – evaluation of 142 observations. *Clin Exp Allergy* 1998; 28:1113–9.
- 10 Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol* 1999; 10:226–34.
- 11 Emmett SE, Angus FJ, Fry JS, Lee PN. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy* 1999; 53:380–5.

- 12 Armstrong D, Rylance G. Definitive diagnosis of nut allergy. *Arch Dis Child* 1999; **80**:175–7.
- 13 Hourihane J O'B, Roberts SA, Warner JO. Resolution of peanut allergy. *BMJ* 1998; **316**:1271–5.
- 14 Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984; **74**:26–33.
- 15 Hourihane J O'B, Kilburn SA, Dean TP, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997; **27**:634–9.
- 16 Yunginger JW, Sweeney KG, Sturmer WQ *et al.* Fatal food-induced anaphylaxis. *JAMA* 1998; **260**:1450–2.
- 17 Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; **327**:380–4.
- 18 Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; **30**:1144–50.
- 19 Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000; **30**:1540–6.
- 20 Pasterello EA, Farioli L, Pravettoni V *et al.* Sensitisation to the major allergen of Brazil nut is correlated with the clinical expression of allergy. *J Allergy Clin Immunol* 1998; **102**:1021–7.
- 21 Bartolome B, Mendez JD, Armentia A, Valverde A, Palacios R. Allergens from Brazil nut: immunochemical characterisation. *Allergol Immunopathol* 1997; **25**.
- 22 Nordlee JA, Taylor SL, Townsend JA, Thomas LA, Bush RK. Identification of a Brazil-nut allergen in transgenic soybeans. *N Engl J Med* 1996; **334**:688–92.
- 23 Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2000; **105**:582–6.
- 24 Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. Peanut allergy: recurrence and its management. *J Allergy Clin Immunol* 2004 Nov; **114**:1195–201.
- 25 Morisset M, Moneret-Vautrin DA, Kanny G *et al.* Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. *Clin Exp Allergy* 2003; **33**:1046–51.