Frequency and significance of immediate contact reactions to peanut in peanut-sensitive children

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Summary

Background Parents of atopic children frequently report, and are alarmed by, contact reactions to foods. Some schools restrict foods due to concerns regarding possible systemic reactions following contact in allergic children.

Objective We aimed to determine the frequency with which peanut-sensitive children exhibited contact sensitivity to peanut butter and to assess the significance of such reactions.

Methods One gram of peanut butter was applied directly to the skin of 281 children who were skin prick test (SPT) positive to peanut (immediate skin application food test; I-SAFT). The test was considered positive if one or more weals were present when the patch was removed after 15 min. A subset of children then underwent an open-label oral challenge with graded amounts of peanut protein.

Results During 3515 clinic visits, 330 I-SAFT tests for peanut contact sensitivity were performed; 136 (41%) were positive. The mean SPT diameter was 10 mm in the I-SAFT-positive children and 8.5 mm in the I-SAFT-negative children (t-test, P < 0.0001). No child had a systemic reaction following topical application of peanut butter. Eighty-four children had 85 oral challenges after blinded, placebo-controlled I-SAFT testing. Challenge was positive in 26/32 of those with a positive I-SAFT and negative in only 6/32. Challenge was also positive in 26/53 but negative in 27/53 of those with a negative I-SAFT (sensitivity 50%, specificity 82%, χ², P = 0.003).

Conclusion A minority of children sensitized to peanut (positive SPT) develop localized urticaria from prolonged skin contact with peanut butter. No tested subjects, including ones with systemic reactions upon oral challenge, developed a systemic reaction to prolonged skin exposure to peanut. Therefore, systemic reactions resulting from this mode of contact with peanut butter appear highly unlikely.

Keywords allergen skin prick test, food challenge, immediate hypersensitivity, immediate skin application food test, peanut, skin contact reaction

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Introduction

The prevalence of peanut allergy is increasing [1] and this allergy usually persists to become a life-long problem [2]. Studies of the general population have estimated the prevalence of sensitization to peanut at around 3% [1], and the prevalence of peanut allergy at between 1% and 1.5% among children [1, 3, 4]. A concern for many parents of children allergic to foods is the risk of an accidental reaction occurring from environmental exposure to food allergens, such as skin contact or inhalation, even when ingestion is unlikely. For this reason, allergenic foods, such as peanut butter, are frequently totally banned from schools and child care facilities because of the perceived risk of a reaction following either skin contact or inhalation of the allergen [5]. If allergenic foods are not banned, then often other measures such as the physical separation of children eating allergenic foods from children with food allergies, or the identification of allergic children with coloured hats or badges, are implemented [6]. Such interventions may have the potential for psychological harm by making food-allergic children feel different from their peers [7, 8]. Even though most accidental reactions at schools occur because of the accidental ingestion of allergens hidden in other foods
not thought to contain the allergen [5], in peanut-allergic subjects systemic reactions to peanut following skin contact with or inhalation of peanut have been reported in retrospective questionnaire or self-report-based surveys [5, 9].

In attempting to address this concern, Simonte et al. [10] reported in a study of a small number of highly peanut-allergic children that a history of a reaction from skin contact or inhalation of peanut was not reproducible under controlled circumstances. Anecdotally, many children presenting to Allergy Clinics who have not had a severe allergic reaction to peanut, and still others who have a positive peanut skin prick test (SPT) only, are often advised to avoid environmental exposure to peanut e.g. sitting at a table where peanuts have previously been consumed. The relevance of a localized reaction following skin contact with peanut, and the risk of a systemic reaction following such an exposure in these groups of children, is not known. Furthermore, peanut is easily removed from children’s hands and from hard surfaces using conventional cleaning techniques and products [11]. And when residual peanut does remain on surfaces after cleaning, the amount has been shown to be below the lowest threshold limits demonstrated to cause systemic reactions following peanut ingestion in peanut-allergic subjects [11].

The atopy patch test (APT), with occlusion times of up to 72 h, has been demonstrated to be a useful test for diagnosing food allergy in children with atopic dermatitis [12, 13]. Seidenari et al. [14] found the APT with peanut to be highly predictive of peanut allergy in children with atopic dermatitis and of delayed reactions to peanut. However, the clinical usefulness of the APT seems to be limited to delayed hypersensitivity reactions. In terms of predicting immediate hypersensitivity reactions, Oranje et al. [15] described a method of applying food directly to the skin, the skin application food test (SAFT), as a diagnostic test for food allergy. The labial food challenge test has also been suggested for the diagnosis of food allergy in children [16]. In this test, a localized or systemic reaction occurring following the application of a drop of food onto a child’s lower lip is said to be diagnostic of food allergy.

This study aimed to determine the frequency with which peanut-sensitive, but not necessarily severely allergic, children exhibit contact sensitivity to peanut butter and the incidence of systemic allergic reactions to peanut following skin contact with peanut butter in these children. We also aimed to determine the predictive value for the outcome of a peanut food challenge of a skin contact reaction to peanut in peanut-sensitive children.

Methods

Study design

An observational and prospective nested case–control study was conducted at Sydney Children’s Hospital, a tertiary referral children’s hospital in Sydney, Australia. The Human Research Ethics Committee of our area health service approved the study protocol. Written informed consent was obtained from parents of children enrolled in the case–control part of the study and whose peanut challenge results were included.

Patients and controls

All children referred to the Allergy Clinic at Sydney Children’s Hospital for investigation of suspected peanut allergy were eligible to be included in this study. Peanut SPTs and immediate SAFTs (I-SAFTs) were not conducted specifically for inclusion in the study, but were always part of the routine clinical investigation of the child.

Skin prick testing

SPT was performed using a commercial whole peanut extract 1:10 w/v (Hollister-Stier laboratories LLC, Spokane, WA, USA) with a negative control (glycerol-saline) and a positive control (histamine HCl 10 mg/mL). Usually, the test was performed on the ventral surface of the child’s forearm. Antihistamine medication was withheld for at least 72 h before the test. The resulting weal was measured with a tape measure after 15 min by measuring the longest diameter of the weal (a) and the diameter orthogonal to it (b). The mean of the SPT weal size was then calculated using the formula \(\frac{a+b}{2}\). A skin test 3 mm larger than the saline control was considered to be positive. Most children had SPTs for other foods or aeroallergens concurrently with the peanut SPT but only the peanut SPT result was considered in this study.

Immediate skin application food testing

Children with a positive peanut SPT then underwent an I-SAFT with peanut butter. Initially I-SAFT was performed as a routine on all patients with a positive peanut SPT but later due to time constraints in our clinic I-SAFT was performed more selectively on children who had a history of a reaction to peanut but had not been witnessed to ingest any peanut during those reactions. I-SAFT was performed to determine whether contact sensitivity existed in those children, which might possibly explain the reaction. I-SAFT was performed regardless of the severity of previous reactions to peanut and no child was excluded from having an I-SAFT because of concerns about a systemic reaction. Many children with a history of a reaction but no witnessed ingestion then went on to have an in-hospital peanut challenge to determine whether they did react following ingestion of peanut. All parents of children undergoing I-SAFT gave verbal consent for the procedure. The I-SAFT method used was a modification of
an SAFT method described previously [15]. One gram of peanut butter (Dick Smith’s smooth peanut butter) on a 2.5 cm cardboard square was applied under an occlusive dressing directly to an area of skin free of other lesions or eczema, usually the upper arm. The peanut butter patch was removed after 15 min and the result was read. I-SAFT was scored as positive if any weals were detected in the area under the patch. For approximately 85 I-SAFT tests 1 g, of an emulsifying ointment was used as a placebo and the investigators were blinded to the placement of the peanut butter and placebo for interpretation of the I-SAFT. Once it was clear that no contact reactions to the placebo occurred in any of these children, the use of the placebo was no longer considered necessary.

Peanut challenges

In-hospital open-label peanut challenges were carried out on children with a positive peanut SPT when it was considered to be indicated by the treating physician; none were carried out exclusively for the study. The reasons for performing a challenge included a positive peanut SPT in a child with no history of peanut ingestion; a positive SPT and a history of a reaction following contact with peanut but no witnessed ingestion (regardless of the I-SAFT result); a previous history of peanut allergy but >2 years since the least reaction especially if the SPT size was decreasing; and finally where it was suspected that a previously allergic child had developed tolerance based on history or a negative SPT. In some cases, challenges were performed for children with a clear history of a reaction following ingestion of peanut in order to more clearly define the child’s threshold dose for reaction because this was unclear on history or to determine the risk of a severe reaction following the accidental ingestion of a small amount of peanut. Those with a recent (within 3 months) history of ingestion (with or without a reaction) of an amount of peanut that could easily be estimated were not rechallenged. Children with a history of anaphylaxis were also not rechallenged. All children undergoing challenges had been avoiding peanut before the challenge because of parental concern or because it had never been introduced into their diets and were all free of symptoms such as urticaria and wheeze, which could make interpretation of a challenge difficult.

For the peanut challenges, finely chopped peanut (containing 26% protein) was used. The children were given 0.02, 0.2, 2.0, 3.8 and 5.7 g (11.7 g cumulative; approximately 12 peanuts) at 20–30 min intervals under medical supervision and with an intravenous cannula in situ. The peanut was usually disguised in a food that the child was known to tolerate to make it more palatable to the children e.g. custard, yoghurt, ice-cream, nut-free cereal or a sandwich. The children were observed in hospital for a period of 2 h after the last ingested dose.

The challenge was scored as positive if any cutaneous (urticaria, angio-oedema), gastrointestinal (abdominal pain, nausea, vomiting, diarrhoea), respiratory (hoarse voice, cough, stridor, wheeze) or cardiovascular (hypotension, tachycardia, collapse, shock) reaction(s) occurred within 2 h of ingestion of the last dose. Challenges were scored as negative if no objective reaction had occurred within 2 h of the last dose of peanut. Where necessary, treatment with antihistamine, hydrocortisone, inhaled salbutamol and/or adrenaline was administered. Children who developed signs of peanut allergy on challenge were considered cases and children who did not were considered controls.

Statistical methods

Categorical data were compared using the χ² test. Means were compared using a Student’s t-test and medians using a Mann–Whitney U-test. SPSS version 14.0 for Windows was used for this statistical analysis. GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego CA, USA, www.graphpad.com) was used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and 95% confidence intervals (CIs) for the I-SAFT. A P-value of <0.05 was considered statistically significant.

Results

Two thousand and forty-seven peanut SPTs were performed during 3515 Allergy Clinic visits over a 3-year period from January 2003 to December 2005. Of these 981 (48%) were positive. The range of the peanut SPT weal size for the 981 positive SPTs was 3–23 mm (mean 7.89 ± 3.7 mm).

Children with at least one previous positive SPT to peanut (including the most recent) then underwent an I-SAFT. As a result, 330 peanut I-SAFTs were performed on 281 peanut sensitized (SPT-positive) children during the same period, of which 136/330 (41%) I-SAFTs were positive in 114/281 (41%) of these children after 15 min. Therefore, most children (167/281; 59%) with a positive peanut SPT did not have contact sensitivity to peanut.

The mean SPT weal diameter for all I-SAFT positive children was 10 mm (95% CI 9.4–10.5 mm) and 8.5 mm (95% CI 8–9 mm) for all I-SAFT-negative children (t-test, P < 0.0001). Peanut–specific IgE levels were not available for all children who underwent an I-SAFT and so were not compared.

Eighty-four children who had a positive peanut SPT and an I-SAFT performed then underwent 85 graded in-hospital peanut food challenges as part of a previous study (Wainstein et al. Pediatric Allergy Immunol 2007). Thirty-one of these 84 (37%) children had a positive I-SAFT, with one child having a positive I-SAFT on
two separate occasions within the study period; thus 32 positive I-SAFTs were included in the analysis. For this cohort, the prevalence of a positive challenge was 61% (52/85; Fig. 1). The demographics of the 84 I-SAFT-positive and I-SAFT-negative children who underwent peanut food challenges are given in Table 1. Only a previous allergic reaction to peanut was significantly associated with a positive I-SAFT. The mean SPT weal diameter of the I-SAFT-negative children who underwent challenges was 8.2 mm (95% CI 7.4–9 mm) compared with 9.8 mm (95% CI 8.7–10.9 mm) in the I-SAFT-positive children who underwent challenges (t-test, P = 0.018). The peanut-specific IgE levels were not normally distributed and so the medians were compared. The median peanut-specific IgE level of the I-SAFT-negative children who underwent peanut challenges was 1.08 kU/L (range 0.35 to > 100 kU/L), which differed significantly from the median peanut-specific IgE level of 7 kU/L (range 0.46 to > 100 kU/L) for the I-SAFT-positive children who underwent challenges (Mann–Whitney U, P = 0.003).

There was a statistically significant association between the I-SAFT result and the outcome of a peanut challenge (χ², P = 0.003), and the likelihood ratio of a positive challenge following a positive I-SAFT was 2.75. However, the sensitivity of a negative I-SAFT was 50% (95% CI; 36–64%) and the specificity of a positive I-SAFT was 82% (95% CI; 65–93%) (Fig. 1). In addition, the PPV of I-SAFT was 81% (95% CI 64–93%) and the NPV was 51% (95% CI 37–65%).

During the peanut food challenges, four children with a positive I-SAFT developed life-threatening anaphylaxis, and 26/32 (81%; Fig. 1) children with a positive I-SAFT had systemic reactions of varying severity. Nevertheless, none of the 281 children who had an I-SAFT performed developed systemic symptoms of peanut allergy of any kind following the topical application of peanut butter for the I-SAFT.

Discussion

This study attempts to determine the risk of a systemic allergic reaction to peanut following the topical application of peanut butter to the skin in peanut-sensitive children. Simonte et al. [10] have already shown in a relatively small number of highly peanut-allergic children that systemic reactions following skin contact with or inhalation of peanut butter are extremely unlikely. We chose to study a larger number of children and included both children who merely demonstrated sensitivity to peanut, i.e. a positive peanut SPT, and children who were confirmed as being allergic to peanut, i.e. a positive oral peanut challenge. We did this because anecdotally a diagnosis of peanut allergy is sometimes made on skin tests alone and many of these children are then advised to avoid environmental exposure to peanut because they are considered at risk of a systemic reaction from such an exposure. We sought to determine the risk of a systemic reaction to peanut following skin contact in these children. Furthermore, to determine accurately the sensitivity and specificity of the peanut I-SAFT, i.e. a local contact reaction to peanut, for predicting the outcome of an oral peanut challenge required both peanut-allergic and non-allergic children to undergo peanut I-SAFT. We showed that while many children with peanut sensitivity, as demonstrated by a positive peanut SPT, also have contact sensitivity to peanut, the risk of a systemic reaction following skin contact with peanut butter is negligible. This is supported by the fact that despite applying the peanut butter to the skin of peanut-sensitized children for 15 min compared with 1 min in the previous study [10], no child developed a systemic reaction following the peanut I-SAFT regardless of the outcome of the I-SAFT or of a subsequent oral peanut challenge. Furthermore, even children at risk of anaphylaxis following the ingestion of peanut are unlikely to develop any systemic symptoms from skin contact with peanut. In addition, although contact sensitivity to peanut is associated with the outcome of a peanut food challenge, the sensitivity and specificity of this as a diagnostic test are not adequate to be used by allergists in clinical practice to predict systemic peanut allergy in these children.

The fact that only 41% of peanut-sensitized children (positive SPT) developed a local reaction from skin contact with peanut (positive I-SAFT) suggests that a peanut SPT may actually be a ‘larger’ exposure to peanut than skin contact with 1 g of peanut butter for 15 min. Perhaps this is because the outer layer of the epidermis is broken during the SPT, whereas the I-SAFT is applied to intact skin. Therefore, theoretically, if a peanut-sensitized child
does not develop a systemic reaction during the peanut SPT, they are also not at risk of a systemic reaction from skin contact with peanut butter similar to an I-SAFT, making it unnecessary to perform I-SAFTs to confirm the absence of risk of a systemic reaction from skin contact with peanut. Furthermore, as has already been suggested, the I-SAFT is a poor diagnostic test for peanut allergy. It may have a place to confirm local contact sensitivity where this is suspected from the history as an explanation for the reaction. This is especially important where skin contact at multiple sites e.g. perioral, periorbital and limbs may mimic a systemic reaction involving only the skin. A challenge may then be necessary to determine whether a similar reaction occurs following the definite ingestion of peanut in such children.

It has been shown that the lowest observed adverse effect level for peanut can be very low indeed, with subjective reactions occurring after the ingestion of 100 μg and objective reactions occurring after the ingestion of 1 mg of peanut in some people [17]. Therefore, we suggest that reports of systemic reactions following environmental exposures to peanut may be due to the unwitnessed ingestion of small amounts of peanut in susceptible children. The finding that no systemic reactions occurred during I-SAFT testing in this study, because an occlusive dressing prevented accidental ingestion of the peanut butter in all cases, would seem to support this. However, children with this level of sensitivity are likely to form a very small proportion of the peanut-allergic community, with only about 1% of peanut-allergic people sensitive to doses as low as 1 mg [18] and about 18% to doses <65 mg [18, 19]. Therefore, a small proportion of very young children who might share food or ingest peanut butter from their skin, etc. are probably at risk of a systemic reaction, seemingly from environmental exposures to peanut only, but perhaps more likely because of the unwitnessed ingestion of peanut products during environmental exposures. We would therefore suggest that stringent restrictions on the presence of peanut products in the environment should perhaps be restricted to child care centres or pre-schools and may not be necessary for primary or high school environments [20]. Against this advice, one may argue that there are published reports of skin contact as a cause of peanut reactions in schools [5, 21]. However, these are retrospective, questionnaire-based reports, not supported by our prospectively acquired data. The contention that no peanut ingestion was witnessed by an adult, presumably a teacher in most cases, in up to 75% of reactions occurring from skin contact was given as evidence for the contention that skin contact alone is the cause of the reaction [5]. However, they do report that most reactions occurring from skin contact were mild and comment that ingestion of peanut could not be completely ruled out in all cases. We are unaware of prospective studies addressing this question. It is reasonable to expect that a teacher supervising a class full of small children may easily miss a very small ingestion of peanut. Therefore, we suggest it is erroneous to assume that simply because an adult does not ‘witness’ peanut ingestion in a child with a reaction threshold of <1 mg of peanut, before a systemic reaction occurring, that no ingestion actually occurred. The current study brings into question the necessity for restrictions at primary and high schools such as the general banning of peanut butter that is easily removed through normal cleaning [11] because of concerns relating to the risk of a reaction following skin contact in a peanut-sensitive child. In addition, accidental ingestion of peanut in schools has been shown to occur despite bans [5]. Therefore, schools would be far better off training their staff to recognize and manage acute allergic reactions to foods rather than imposing restrictions that are unlikely to

Table 1. Demographics of the 84 children who underwent peanut food challenges according to their I-SAFT status

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>I-SAFT positive, n = 31</th>
<th>I-SAFT negative, n = 53</th>
<th>P = 0.36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SEM</td>
<td>4.15 ± 0.55</td>
<td>4.73 ± 0.37</td>
<td></td>
</tr>
<tr>
<td>Sex (n)</td>
<td>Boys 17</td>
<td>36</td>
<td>P = 0.23</td>
</tr>
<tr>
<td></td>
<td>Eczema 24</td>
<td>40</td>
<td>P = 0.84</td>
</tr>
<tr>
<td></td>
<td>Allergic rhinitis 9</td>
<td>23</td>
<td>P = 0.19</td>
</tr>
<tr>
<td></td>
<td>Any atopy**</td>
<td>30</td>
<td>P = 0.42</td>
</tr>
</tbody>
</table>

*P < 0.05.
1t-test.
2χ² test.
3History of previous contact with peanut – ingestion or skin contact if no ingestion witnessed.
4History of an allergic reaction to peanut in children previously exposed to peanut.
5Documented allergic reaction and/or positive SPT to foods other than peanut.
6One or more of asthma, eczema or food sensitivity/allergy.
SPT, skin prick test; I-SAFT, immediate skin application food test.
effectively protect allergic children anyway. Studies have shown that despite a large proportion of schools having at least one nut-allergic child, many schools in the USA and UK are very poor at recognizing and managing acute allergic reactions to food [5, 22].

An alternative explanation for the reported systemic reactions from skin contact with peanut may be that those exposures were to unusually high concentrations of peanut e.g. an entire class using peanut for a craft activity [5, 10]. Such exposures are unlikely to occur in most situations of daily life at primary or high schools, e.g. sitting near another child eating a peanut product, suggesting once again that excessive restrictions because of this perceived risk should be avoided. Another possible reason why our findings differ from previous reports may be that we used a non-volatile form of peanut i.e. peanut butter and that other forms of peanut e.g. cooking peanut in sauces are more likely to cause inhalation reactions in susceptible people. However, the proportion of peanut-allergic people with reaction thresholds low enough to place them at risk from such exposures is once again likely to be very small. And finally the accidental transfer of peanut butter to areas distant from the site of initial skin contact, e.g. the eye, may give the impression of a systemic reaction from skin contact. Some reports may not adequately differentiate between contact reactions and true systemic reactions, thus overrepresenting the risk of systemic reactions from skin contact with peanut. This is especially true for self-reported events by parents or patients that are not controlled or witnessed by medical professionals.

We further wondered whether the findings of our study do not support the notion that systemic reactions can occur from environmental contact with peanut because we chose to apply the peanut butter to the child’s arm and not a mucosal surface. In the paper by Rance and Dutau [16] on labial food challenges, they suggest that a localized, or in a few cases, systemic reaction following the application of a drop of food to which the patient has demonstrated IgE to the lower lip indicates a diagnosis of food allergy. However, in that study, atopic dermatitis was considered to be suggestive of food allergy in 61% of cases and 94% of patients manifested contiguous urticaria or milder reactions as their reaction to a labial challenge. From the current study, it is apparent that local reactions may not predict systemic reactions and none of the patients with a positive labial challenge test in the study by Rance and Dutau [16] were given an oral challenge to confirm that they would develop systemic symptoms on ingestion of the food. One could argue that application of the food to the lip rather than a distant site like the arm is more predictive of what might occur following ingestion. However, Rance and Dutau [16] actually comment that the labial challenge test differs from the sublingual test in that it reduces that risk of systemic absorption of the allergen.

In addition, they placed a swab between the lip and the gums to reduce systemic absorption of the food. Therefore, the labial challenge test would seem very similar to applying the food to a more distant site and therefore may not always be predictive of a systemic reaction following ingestion, with the only advantage being the ease of observing subtle swelling around the lips rather than on the skin.

In conclusion, we suggest that the risk of a systemic reaction from skin contact with peanut in peanut-sensitive people is low and that such contact reactions should not be used to predict the likelihood of systemic allergy to peanut following peanut ingestion.

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