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Title: The Natural History of Peanut Sensitization and Allergy in a Birth Cohort.

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Capsule summary

In this birth cohort, peanut allergy started in early childhood and persisted until young adult life. Allergic sensitization to peanut rose gradually from early childhood, with a rapid increase during adolescence; the latter being mostly asymptomatic.

Key Words:

Peanut Allergy, peanut allergen sensitization, natural history, birth cohort

To the editor,

Information on the natural history of peanut allergic sensitization (PAS) and clinical peanut allergy (PA) remains limited. Most previous studies selected children who were diagnosed with PA, which does not provide the population perspective and probably ignores those with low levels of sensitization.[1,2] There are no population based studies on the natural history of PAS or PA. To provide a population perspective, we used the Isle of Wight (IoW) birth cohort (n=1,456) and determined the natural history of PAS and PA, focusing on incidence, persistence and remission. At 1, 2, 4, 10 and 18 years, validated questionnaires were completed to obtain information on allergic symptoms, including peanut allergic reactions. Skin prick test (SPT) were carried out to 14 aero- and food allergens, including peanut at ages 4, 10 and 18 years in all consenting participants and at 1 and 2 years in those with allergic symptoms.[3] Allergic sensitization was defined as a mean weal diameter of 3 mm greater than the negative control to an allergen on SPT. The diagnosis of PA was based on a convincing clinical history (one or more recognized allergic symptoms developing within 2 hours of food ingestion) plus evidence of sensitization to peanut on SPT. We used the term PAS, where SPT was positive to peanut irrespective of clinical reactivity.

Details of experimental methods used and statistical analyses are provided in the online supplement of this article. Briefly, prevalence and their 95% confidence intervals were calculated. Means of SPT wheal sizes in those with persistent and remittent sensitization were compared using T test. Figure E1 (see online repository) provides information on data at each assessment. Details of each child sensitized to peanut at age 4, 10 and 18 years is provided in table E1, while table E2 provides a complete picture with imputed data (see online repository).

PAS increased gradually in the first decade of life but showed a steeper rise from 10 to 18 years (Fig 1a). At age 4 years, 13 of 976 children (1.3%, 95% confidence intervals (CI): 0.8%-2.3%) were

sensitized to peanut. This increased to 19 of 1034 (1.8%, 95% CI: 1.2%-2.9%) at age 10 years with a further increase to 54 out of 851 (6.4%, 95% CI: 4.9-8.2%) at age 18 years. Previous studies have reported a similar prevalence of PAS varying from 1.1% to 8.6%.[4,5] We show that this is primarily age dependent and varies from 1.3% in early childhood to 6.8% in adolescence (Fig 1b). At age 1 and 2, only those children reporting allergic symptoms were skin prick tested and hence the prevalence could have been overestimated. However, prevalence figures at age 1 and 2 are similar to those reported previously in another unselected birth cohort on the IoW.[6] All peanut sensitized children had positive reactions to at least one aeroallergen with grass pollen sensitization being more common than tree pollen (Table E3). Cross-reactivity of peanut and grass pollen has been reported previously.[7] At 4 years, eczema was the major co-morbidity, while at 10 and 18 years, rhinitis was present in the majority of peanut sensitized children.

The most common pattern of peanut sensitization was its development for the first time at 18 years; in 42 of 66 children (63.6%, 95% CI: 51.6%-74.2%) in association with grass pollen sensitivity and allergic rhinitis (Table 1 & E3). The other common pattern was persistent sensitization from age 4 (n=9) or 10 (n=6) years (15 of 66 or 22.7%, 95% CI: 14.3%-34.2%). However, other patterns where sensitization was transient or recurrent were observed in 9 of 66 (13.6%, 95% CI: 73.5%-23.9%) children. The mean difference in wheal size of 1.1 mm between persistence (mean; 4.4, SD: 2.0) and transient group (mean; 3.3, SD: 0.4) failed to reach statistical significance (p=0.06).

There was minimal change in the overall prevalence of PA beyond early childhood and it remained around 0.6% (Fig 1b). New onset of PA was uncommon at 10 years (1 of 6) but more common at 18 years (3 of 6). Remission of PA was seen in 1 of 6 (17%) between ages 4 to 10 years and 1 of 4 (25%) from age 10 to 18 years (Table E4). The numbers with PA in our study were small and therefore, these findings should be interpreted with caution. However, the development of natural tolerance in a

small proportion is consistent with previous reports.[1] We did not observe recurrence of PA, although one patient had recurrence of PAS after initial loss of SPT reactivity (Table 1).

The diagnosis of PA can be questioned as oral challenge was not performed. However, a history of acute clinical reaction and evidence of allergic sensitization is considered adequate for the diagnosis in most cases.[8] Moreover, we have previously shown that even a 3mm wheal has about 75% positive predictive value for PA if symptoms are present.[9] Another limitation was missing information for SPT, which is inevitable in a long-term study, which spans over 20 years.

Sensitization to peanut in early childhood was more commonly associated with clinical reactivity than during adolescence. Of those with sensitization at 4 year (n=10), 4 (40%) developed PA, while at age 18, only 2 of 42 (4.76%) children with new-onset sensitization developed PA (P=0.009). Thus, the increase in the number of subjects sensitized to peanut during adolescence was largely due to the onset of asymptomatic sensitization.

In summary, in this cohort, PA started early in childhood and persisted in most children until adult life. A few adolescents did have new-onset PA compensating for those who remitted and therefore the overall prevalence remained around 0.6%. The natural history of PAS differed from that of PA in that it increased gradually from early childhood, with a significant peak incidence during adolescence. Most of this new onset sensitization to peanut was asymptomatic and associated with pollen sensitization and allergic rhinitis. The numbers with peanut allergy were small and thus generalizability of these findings is uncertain. Similar assessments in other longitudinally followed birth cohorts will clarify developmental patterns of PAS and PA during childhood.

Contributors

SHA generated the original hypothesis and all authors contributed to study design. SHA, GR and RJK were responsible for all allergy phenotype data collection. CV and TD advised on analysis and interpretation of the data. SHA wrote the first draft of the manuscript, and all authors have seen and approved the final version of the report. SHA will serve as guarantors for its contents.

Conflict of interest statement

None of the authors have any conflicts of interests to declare.

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References

1. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. J Allergy Clin Immunol 2001; 107:367-74.
2. Savage JH, Limb SL, Brereton NH, Wood RA. The natural history of peanut allergy: Extending our knowledge beyond childhood. J Allergy Clin Immunol 2007; 120:717-9.
3. Roberts G, Zhang H, Karmaus W, Raza A, Scott M, Matthews S, et al. Trends in cutaneous sensitization in the first 18 years of life: results from the 1989 Isle of Wight birth cohort study. Clin Exp Allergy 2012; 42:1501-9.
4. Arbes SJ, Jr., Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol 2005; 116:377-83.
5. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 2007; 120:638-46.
6. Dean T, Venter C, Pereira B, Arshad SH, Grundy J, Clayton CB, et al. Patterns of sensitization to food and aeroallergens in the first 3 years of life. J Allergy Clin Immunol 2007; 120:1166-71.
7. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol 2010; 125:191-7 e1-13.
8. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J Allergy Clin Immunol 2010; 126:1105-18.

9. DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. J Allergy Clin Immunol 2011; 127:633-9.e1-3.

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145 **Figure Legend**

146 **Figure 1a: Sensitization to peanut on skin prick test from 1 to 18 years of age.**

147 Sensitization was defined as a positive SPT to peanut. Numbers above each point represent % of

148 participants with sensitization at each assessment point.

149

150 **Figure 1b: Clinical allergy to peanut from 1 to 18 years**

151 Clinical allergy to peanut was defined as appearance of typical type I hypersensitivity symptoms within 2

152 hours of exposure to peanut in participants with sensitization on SPT. Numbers above each point

153 represent the % of participants with peanut allergy at each assessment.

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Table 1: Natural history of sensitization to peanut during childhood.

	Sensitized subjects	SPT size at 4 year	SPT size at 10 year	SPT size at 18 year
Pattern of sensitization	N=66	Median (IQ range 25-75)	Median (IQ range 25-75)	Median (IQ range 25-75)
+++	9 (13.6%)	3.5 (3.0-6.0)	4.5 (3.0-7.5)	5.50 (4.6-9.3)
-++	6 (9.1%)	0	3.5 (3.0-5.3)	3.50 (3.4-4.3)
--+	42 (63.6%)	0	0	4.0 (3.3-4.6)
++-	2 (3.0%)	3.3 (3.0-3.5)	4.50 (3.0-6.0)	0
+--	4 (6.1%)	3.0 (3.0-3.8)	0	0
+-+	1 (1.5%)	4.0	0	3.8
-+-	2 (3.0%)	0	3.0 (3.0-3.0)	0

On-line Supplement

METHODS:

Study setting:

An unselected whole population birth cohort (n=1,536) was recruited in 1989 to prospectively study the natural history of allergic diseases. After exclusion of adoptions, perinatal deaths and refusal for follow-up, 1,456 children were enrolled with follow-up assessments conducted at 1, 2, 4, 10 and 18 years.[E1-E5] The study was approved by the local ethics committee before recruitment and for each assessments. Informed consent was obtained from parents at age 1, 2, 4, 10 and from participants at age 18 years.

Assessments:

At each stage, validated questionnaires were completed to obtain information on allergic symptoms, including peanut allergic reactions. Questions about eating nuts were asked at age 4, 10 and 18 years. SPT were carried out to 14 aero- and food allergens, including peanut at ages 4, 10 and 18 years in all consenting participants and at 1 and 2 years in those with allergic symptoms (ALK-Abello, Horsholm, Denmark) as described before. Histamine (0.1 %) and physiological saline were used as positive and negative controls. A mean weal diameter at least 3 mm larger than that seen with saline after 15 minutes was taken as a positive result.

Definitions

Allergic Sensitization: Allergic sensitization was defined as a mean weal diameter of 3 mm greater than the negative control to an allergen on SPT. Results were discounted if the positive control was not at least 3 mm in diameter.

Peanut allergic sensitization (PAS): SPT positive to peanut irrespective of clinical history of a reaction.

Clinical peanut Allergy (PA): The diagnosis of PA was based on a convincing clinical history verified by an allergist (SHA, RK, GR) plus evidence of allergic sensitisation to peanut. We required all 3 of the following criteria to be met;

1. The report of one or more recognized allergic symptoms such as:[E6]
    a) localized: itching, sting/ burning of the lips/ mouth or throat, urticaria/ hives, angioedema
    b) abdominal: nausea, vomiting, crampy/ colicky abdominal pain, diarrhea
    c) respiratory: wheeze, stridor, watery rhinitis, redness of eyes/ nose
    d) skin: urticaria, itching, flushed skin, worsening eczema
    e) systemic reaction: anaphylaxis
2. Temporal relationship of a reaction with symptoms developing within 2 hours of food ingestion.
3. Positive SPT to peanut.

Asymptomatic sensitization to peanut: Where SPT was positive to peanut but there was no evidence of a clinical reaction to peanut.

Asthma: At 4 year follow-ups, the medical investigator determined the presence of asthma based on wheeze over the last 12 months and treatment given for asthma or asthma related symptoms. At the 10 and 18 year follow-ups, asthma was defined as having “physician diagnosed asthma” and either “wheezing or whistling in the chest in the last 12 months” or “current treatment for asthma”, following the International Study of Asthma and Allergies in Childhood (ISAAC) criteria.[E6]

Rhinitis was defined by an affirmative answer to “have you ever had a problem with sneezing, runny or blocked nose in the absence of cold or flu” plus “symptoms in the last 12 months”.[E6]

Eczema was defined as chronic or chronically relapsing, itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution, following Hanifin and Rajka criteria.[E7]

Statistical analysis

Data were analysed using SPSS version 9. Means of SPT wheal sizes in those with persistent and remittent sensitization were compared using T test. Children were regarded as having “any sensitization to peanut” if SPT was positive to peanut at one or more assessment. When children developed PAS or

PA at 2 or 4 years, this was regarded as “Early childhood”. To provide a complete picture, data were imputed, replicating adjacent sensitization data, as shown in Table E2. Thus, missing data at 4 and 18 years were imputed by that at 10 years (when most children were seen and had skin test.

Table E1: Natural history of sensitization to peanut during childhood (individual results).

Subjects	4 year	10 year	18 year
	Skin prick test mean wheal diameter (in mm)		
1	6.0	4.5	4.75
2	3.5	3.0	5.0
3	6.0	6.0	9.0
4	3.0	4.5	5.5
5	4.0	7.0	10.5
6	3.0	8.0	Missing
7	10.0	9.5	Missing
8	Missing	3.0	4.5
9	Missing	3.0	3.25
10	0	6.0	3.5
11	0	3.0	6.0
12	0	5.0	3.5
13	0	3.5	3.75
14	0	3.0	Missing
15	0	3.5	Missing
16	3.5	6.0	0
17	Missing	3.0	0
18	4.0	0	0
19	3.0	0	0
20	3.0	0	0
21	3.0	0	Missing
22	4.0	0	3.75
23	0	3.0	0
24	0	3.0	0
n=42*	13 missing	7 missing	3.0 – 7.5

*At the age of 18 years, 42 subjects had new onset sensitization. However, 13 of these were not seen age 4 years and 7 were not seen at age 10 years.

Table E2: Natural history of sensitization to peanut during childhood (individual results; with imputation of missing data)

Subjects	4 year	10 year	18 year	Pattern
	Skin prick test mean wheal diameter (in mm)			
1	6.0	4.5	4.8	+++
2	3.5	3.0	5.0	+++
3	6.0	6.0	9.0	+++
4	3.0	4.5	5.5	+++
5	4.0	7.0	10.5	+++
6	3.0	8.0	8.0	+++
7	10.0	9.5	9.5	+++
8	3.0	3.0	4.5	+++
9	3.0	3.0	3.3	+++
10	0	6.0	3.5	-++
11	0	3.0	6.0	-++
12	0	5.0	3.5	-++
13	0	3.5	3.8	-++
14	0	3.0	3.0	-++
15	0	3.5	3.5	-++
16	3.5	6.0	0	++-
17	3.0	3.0	0	++-
18	4.0	0	0	+--
19	3.0	0	0	+--
20	3.0	0	0	+--
21	3.0	0	0	+--
22	4.0	0	3.8	+-+
23	0	3.0	0	-+-
24	0	3.0	0	-+-
N=42*	0	0	3.0-7.5	--+

*Those 42 subjects who had new onset sensitization at the age of 18 years were grouped together.

Note: Imputation of missing data: For the first 24 subjects, missing data at 4 and 18 years were imputed by that obtained at 10 years. For those with new onset sensitization (n=42) at age 18 years, missing SPT at age 4 and 10 years were presumed to be negative and regarded as zero.

Table E3: Associated allergic sensitization and clinical allergic conditions in those with peanut sensitization at each age.

	4 year	**10 year**	**18 year**
Peanut sensitization	N=13	N=19	N=54
Sensitization to any aeroallergen	11 (84.6%)	17 (89.5%)	52 (96.3%)
Sensitization to grass pollen mix	6 (46.2%)	12 (63.2%)	47 (87.0%)
Sensitization to tree pollen mix	Not done	3 (15.8%)	27 (50.0%)
Sensitization to any food allergen	3 (23.1%)	5 (26.3%)	48 (88.9%)
Sensitization to wheat	0	3 (15.8%)	47 (87.0%)
Sensitization to soya	1 (7.7%)	1 (5.3%)	4 (7.4%)
Asthma	6 (46.2%)	6 (31.6%)	23 (42.6%)
Eczema	8 (61.5%)	6 (31.6%)	7 (13.0%)
Rhinitis	3 (23.1%)	10 (52.6%)	47 (87.0%)

Table E4: Natural history of clinical peanut allergy

Subjects	4 year	10 year	18 year	Nature of worst allergic reaction
1	PA	PA	PA	Oral symptoms, vomiting, urticaria and anaphylaxis
2	PA	PA	PA	Anaphylaxis within an hour of peanut ingestion
3	PA	PA	PA	Vomiting within an hour of peanut ingestion
4	PA	PA	Missing	Urticarial rash within one hour of peanut ingestion
5	PA	PA	No PA	Urticarial rash and throat tightness within an hour of peanut ingestion
6	PA	No PA	No PA	Urticaria within an hour of peanut ingestion
7	No PA	AS	PA	Immediate throat tightness, wheezing, generalized urticaria, anaphylaxis
8	No PA	No PA	PA	Urticaria and wheeze, progressing to anaphylaxis
9	No PA	No PA	PA	Anaphylaxis
10	AS	PA	Missing (died)	Immediate vomiting with peanut; died at age 11 of acute asthma attack[E9]

PA= Peanut Allergy
No PA= No Peanut Allergy
AS= Asymptomatic sensitization
Notes: Out of 6 cases of PA at age 4 years, 5 persisted to 10 years and one outgrew PA. Of these 5, 3 had persistent allergy to 18 years (one was not seen at 18 years and one outgrew PA).
Allergic reaction to peanut caused typical symptoms including systemic manifestations or anaphylaxis.
One child at 4, 2 at 10 and 4 at 18 years had given a history of anaphylactic reactions to peanut.
All of these children had been given a diagnosis of asthma, eczema and rhinitis at some stage in their life except one child (subject 7 in Table 4) who did not have eczema.

References

E1. Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. J Allergy Clin Immunol 1992; 90:235-41.

E2. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. Clin Exp Allergy 1993; 23:504-11.

E3. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. J Allergy Clin Immunol 1998; 101:587-93.

E4. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. Clin Exp Allergy 2003; 33:573-8.

E5. Scott M, Raza A, Karmaus W, Mitchell F, Grundy J, Kurukulaaratchy RJ, et al. Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. Thorax 2010; 65:258-62.

E6. Niggemann B. When is an oral food challenge positive? Allergy 2010; 65:2-6.

E7 Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995 Mar;8(3):483-91.

277 E8. Hanifin JM, Rajka G (1980) Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl
278 (Stockh) 92: 44-47.
279
280 E9. Kurukulaaratchy RJ, Matthews SM, Arshad SH. The natural history of fatal childhood asthma--a
281 case from the Isle of Wight Birth Cohort. J Asthma 2008; 45:944-7.
282