

The prevalence of peanut sensitization and the association to pollen sensitization in a cohort of unselected adolescents – The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS)

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In the last decade an increased occurrence of peanut hypersensitivity and severe anaphylactic reactions to peanut have been reported. However, few prevalence studies have been performed in unselected populations. This study evaluated the point prevalence of peanut hypersensitivity in Danish adolescents. The point prevalence of peanut allergy confirmed by oral challenge was estimated to 0.5%. The number of adolescents sensitized to peanut by specific immunoglobulin E (IgE) (CAP FEIA) and skin prick test (SPT) were higher (5.8% resp. 3.4%). In adolescents without clinically relevant peanut sensitization most cases were sensitized to grass pollen and the IgE class for grass was higher than for peanut. A correlation between peanut and pollen (grass) sensitization is therefore plausible. Before a positive SPT or specific IgE measurement to peanut is considered clinically relevant in a patient, the case history should be evaluated together with examination for pollen sensitization.

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During the last decade an increasing prevalence of peanut hypersensitivity has been reported (1). Peanuts are one of the most common foods causing allergic reactions both in children and adults (2). Furthermore, peanuts are one of the most common foods responsible for food-induced anaphylaxis (3). Several case reports from UK and USA have been published about severe anaphylactic reactions to peanut (3, 4). The prevalence of self-reported peanut allergy is estimated to 0.5–1% in unselected populations of children and adults (5–7). Zuberbier et al. (8) newly published a study from Berlin where 2.6% of the population had positive skin prick tests (SPT) to peanut. The perceived prevalence of food allergies is substantially higher than the real

prevalence (9), and studies using oral challenge to confirm the present of peanut allergy in unselected populations are sparse (1).

Cross reactivity between pollinosis and allergy to fresh fruits and vegetables have been described for several food allergens (10). Frequently, the occurrence of cross-reactive immunoglobulin E (IgE) antibodies is not correlated with development of clinical food allergy (11). Cross-reaction between grass pollen and peanuts has been suggested in few studies (12). However, the clinical implication remains unknown. So far no studies have shown a clear-cut relation between peanut and pollen sensitization.

The aim of this investigation was to estimate the prevalence of peanut sensitization in an

unselected population of adolescents and to evaluate the clinical relevance of a positive specific IgE/SPT to peanut and the possible correlation between peanut and pollen sensitization.

Methods

Population and study design

The Odense adolescence cohort study (TOACS) is an epidemiological follow-up study. Phase 1 (1995–96) was conducted as a cross-sectional study among 1501 eighth grade school children (mean age 14.1 yr) in 40 of 43 schools in the municipality of Odense, Denmark and included questionnaire, interview, and clinical examination, blood sampling for IgE measurements, and diagnostic patch tests.

Phase 2 (1996–97) was a case-control study among 702 of the school children and included interview, clinical examination, and SPTs. The population and study design both in phases 1 and 2 have been described in details previously (13, 14).

Subsequently, adolescents with a positive specific IgE measurement against peanut were interviewed by phone about the relevance of a positive test. Those with a positive SPT against peanut were interviewed immediately after skin test. The peanut sensitized (positive CAP FEIA or SPT) was invited to further examination including repeated interview, SPTs, blood sample for IgE measurements, and histamine-release (HR) measurements. The total number of adolescents participating in CAP FEIA/SPT was 979. Those with a positive case history for peanut allergy were offered a double-blind placebo controlled food challenge (DBPCFC) with peanut whereas those with a negative case history had an open challenge. This part of the study took place in 1999.

Definitions and description of terms

Atopic dermatitis (AD). The lifetime prevalence (birth to present age) of AD was defined by published questionnaire criteria where the diagnosis is based on summation of 17 questions (15).

Allergic asthma and allergic rhinitis (inhalant allergy). The lifetime prevalence of inhalant allergy (allergic asthma and/or allergic rhinitis) was evaluated from the interview of the school children.

Asthma was defined as three or more episodes of wheezing/whistling in the chest and/or dyspnoea and/or cough. Allergic asthma was defined as three or more episodes of symptoms either at exposure to known allergens (pollen, animal

dander, house dust mite, mold, food) or in certain periods (seasonal variation, diurnal variation, inside/outside).

Rhinitis was defined as one or more of the following symptoms: Itching in the nose, watery rhinorrhoea, sneezing, and nasal congestion (16). Allergic rhinitis was defined as one or more symptoms either at exposure to known allergens or in certain periods or continuing for at least 2 wk without infectious rhinitis or other infections. Allergic rhinitis was separated in intermittent and persistent rhinitis (17).

IgE measurements

All serum samples were stored at -20°C until analysis. The total and specific IgE measurements were performed using the Pharmacia CAP FEIA System® (Pharmacia & Upjohn, Uppsala, Sweden).

Sera from the school children in phase 1 were tested for specific IgE antibodies against inhalant allergens, food allergens and *pityrosporum ovale*. A screening strategy was applied: Series with inhalant allergens (Phadiatop®) and food allergens (fx1, fx5) were performed and only positive samples were subjected to further analyses with the individual allergens. All analyses were performed in duplicates and results expressed as mean. The maximal deviation on the two measurements was 10%. A serum level higher than 0.35 kU/l (corresponding to class 1) for specific IgE was considered as positive.

The peanut sensitized gave a new blood sample after phase 2 and this blood sample was analyzed for pollen [birch, grass (timothy), mugwort], Latex, peanut, wheat flour, soy bean, hazelnut, green bean and green pea.

Skin prick tests (SPT)

The SPTs in phase 2 were carried out with 19 commercially available allergen extracts (Soluprick®) from ALK-ABELLO, Hørsholm, Denmark and with three fresh foods. A positive control (Histamine dihydrochloride 10 mg/ml) and a negative control (Soluprick solution) were included. Prick test extracts from the same batches were used during the whole study.

Before the SPTs short-acting antihistamines were discontinued for at least 4 days and long-acting antihistamines, e.g., astemizole for at least 4 wk. Topical corticosteroids were discontinued at least 1 wk prior to the SPTs. The SPT was performed according to EAACI guidelines (18).

The allergen extracts in phase 2 comprised inhalant allergens, food allergens and malazessia

furfur/pityrosporum ovale. The fresh foods consisted of wheat flour and Soya flour diluted in NaCl (1:10) and fresh apple.

The peanut sensitized were SPTed again including extracts with pollen [birch, grass (timothy), mugwort], Latex and peanut and a panel of fresh unprocessed foods including peanut, wheat flour, soy bean, hazelnut, green bean and green pea.

Histamine release (HR)

The HR was performed after phase 2 and included extracts with pollen [birch, grass (timothy), mugwort], Latex and peanut and fresh peanut, wheat flour, soya bean, hazelnut, green bean and green pea. HR was performed using glass-fibre-based histamine assay including six allergen dilutions of each allergen in duplicate (<http://www.reflab.dk>) (19).

Open challenge and DBPCFC

The open challenge was performed with 50 g peanut and the adolescents were observed for 2 h.

The DBPCFC was performed by masking peanut in a chocolate bar using titrated doses (20). The total content of peanut in the chocolate bar was 50 g. The bar was divided into seven pieces, the first contained 0.16 g peanut, the following 0.32, 1.28, 2.56, 5.12, 10.24 and 30.50 g. The school children were observed 15 min between each dose and were observed 2 h after the last dose. The procedure was essentially according to the new EAACI guidelines (21).

Ethics

The ethics committee for Vejle and Funen County approved the study (case number 95/22). Informed consent was obtained both from the school children and their parents.

Statistics

All data have been entered twice in the database; when differences were found, a comparison with raw input forms was made and corrections done accordingly. All statistical analyses were performed with Stata 5.0 for Windows 95 (Stata corporation, TX, USA).

To compare CAP FEIA results for grass and peanut the Wilcoxon matched pairs signed rank sum test was applied and Spearman's rank

correlation coefficient given. Values were considered significant at the $p < 0.05$ level.

Results

Peanut sensitization

The prevalence of peanut sensitization in phase 1 was 5.8% (50/862) using CAP FEIA (26% class 1, 54% class 2, 18% class 3 and 2% class 4).

A positive case history was found in 11% (5/45) of the peanut sensitized school children (five could not be reached by phone).

Of the 45 peanut sensitized school children 60% reported that they had eaten peanuts during the last month and 87% had ingested peanuts during the last 12 months. Sixty-nine per cent ate more than five peanuts the last time they were exposed.

In phase 2 3.4% (19/558) of the cases and controls were sensitized to peanut using SPT. A positive case history was reported by 21% (4/19).

A total of seven school children had a positive case history and were either sensitized in SPT or CAP FEIA. All seven reported oral allergy syndrome as the initial symptom upon ingestion, one also asthma, one urticaria, and gastrointestinal symptoms and one exacerbation of AD. No history of severe reactions was recorded.

Oral food challenge

Oral food challenges were offered to 61 adolescents who had a positive CAP FEIA or SPT to peanut, and the participation rate was 44% (27/61).

Open challenge was performed in 22 cases with a positive CAP FEIA/SPT to peanut but negative case history. The open challenge was negative in all cases.

DBPCFC was performed in five adolescents with a positive CAP FEIA/SPT to peanut and a positive case history and were positive for 2 of the 5.

Clinically relevant peanut hyper sensitization was found in 7.4% (2/27) of the adolescents with a positive CAP FEIA/SPT to peanut. Extrapolating this to the 61 adolescent with a positive CAP FEIA/SPT to peanut 4–5 ($7.4 \times 61/100$) of the adolescents had clinically relevant peanut hyper sensitization. The total number of adolescents participating in CAP FEIA/SPT was 979. An estimate of clinically relevant peanut hyper sensitization for the cohort would therefore be 0.5% (4.5/979).

No reaction to placebo was seen.

Description of peanut allergic adolescents

Case 1. A girl with AD and intermittent rhinitis: She had a positive SPT to both fresh peanut and commercial extract and CAP FEIA was class 2, but a negative HR test was found. By DBPCFC subjective symptoms were registered after first dose (0.16 g), but objective signs of oral allergy syndrome were first registered after the last dose (50 g total).

Case 2. A girl with AD, intermittent rhinitis and allergic asthma: She had a positive SPT to both fresh peanut and extract, and CAP FEIA was class 2 and she also had a positive HR test. By DBPCFC subjective symptoms were registered after first dose (0.16 g) and objective signs of oral allergy syndrome were registered after the second dose (0.48 g).

Peanut sensitization in relation to atopic diseases and pollen sensitization

Most of the peanut sensitized had atopic diseases (Table 1). Peanut sensitization was a characteristic finding among those with intermittent rhinitis. Among school children sensitized to peanut in CAP FEIA nearly all (96%) had a concomitant reaction to grass pollen (Fig. 1). The same

Table 1. Peanut sensitization in relation to atopic diseases

	Peanut sensitization	
	CAP FEIA (n = 50)	SPT (n = 19)
Atopic diseases	68% (34/50)	100% (19/19)
Intermittent allergic rhinoconj.	58% (29/50)	74% (14/19)
Persistent allergic rhinoconj.	24% (12/50)	32% (6/19)
Asthma	22% (11/50)	42% (8/19)
Atopic dermatitis	44% (22/50)	79% (15/19)

SPT, skin prick test.

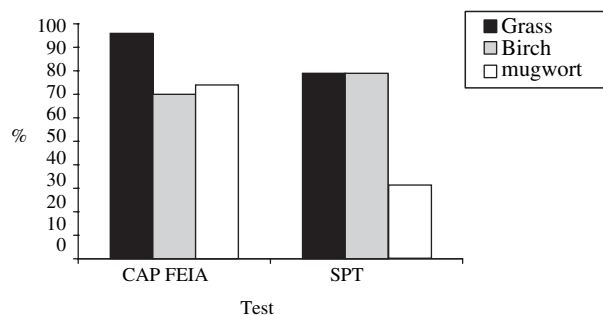


Fig. 1. Concomitant reaction to pollen [CAP FEIA, skin prick test (SPT)] in peanut sensitized adolescents.

Table 2. Specific immunoglobulin E (IgE) class for peanut against grass pollen

Grass (specific IgE class)	Peanut (specific IgE class)				
	0	1	2	3	4
0	705	1**	1*	0	0
1	21	6	0	0	0
2	37	1	6	0	0
3	29	2	2	2	1*
4	20	3	18	7	0

*Relevance for peanut, specific IgE for birch (class 4), clinical atopy.

**Specific IgE for peanut, almond, wheat, cladosporium with no relevance, atopic dermatitis.

$p < 0.0001$ (the Wilcoxon matched pairs signed rank sum test).

Spearman's rank correlation coefficient 0.53 ($p < 0.0001$).

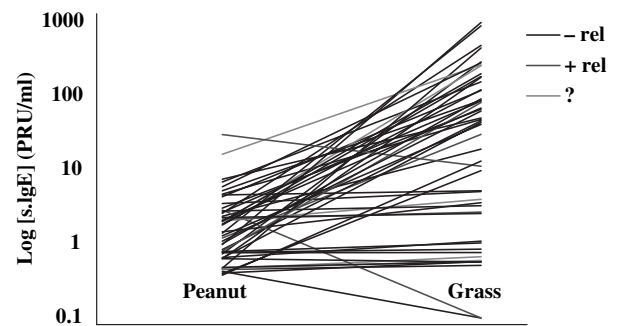


Fig. 2. Concentration of specific immunoglobulin E (IgE) (log) to peanut and grass for the school children with elevated specific IgE to peanut. Notes: -rel, no clinical relevance of a positive CAP FEIA to peanut; +rel, clinical relevance of a positive CAP FEIA to peanut; ?, clinically relevance not evaluated. $p < 0.0001$ (the Wilcoxon matched pairs signed rank sum test) and Spearman's rank correlation coefficient 0.53 ($p < 0.0001$).

was found among the peanut sensitized in the SPT (Fig. 1).

By plotting specific IgE class for peanut against grass there is a tendency of having a higher IgE class for grass compared to peanut in all school children except for three (Table 2). Two of these three had a clinically relevant peanut hypersensitivity and the third had a total IgE level of 6303, several unspecific IgE results and had AD. Fig. 2 shows the same picture by plotting concentrations (log) of specific IgE (PRU/ml) to peanut and pollen in peanut sensitized adolescents. The result was verified by using the Wilcoxon matched pairs signed rank sum test ($z = -11.47$, $p < 0.0001$) and the Spearman's rho was estimated to 0.53 ($p < 0.0001$).

Discussion

The prevalence of peanut sensitization in unselected Danish adolescents evaluated by CAP FEIA and SPT was high (5.8% resp. 3.4%).

However, the reaction was clinically relevant only in selected cases. The point prevalence of peanut allergy confirmed by oral challenge was estimated to 0.5%.

Questionnaire and interview based studies from USA, UK and France have estimated the prevalence of peanut allergy to 0.5–1% of the population (5–7). However, questionnaire based surveys are likely to overestimate the prevalence because self-reported food allergies are generally higher than can be proven by oral challenge (9). A cohort study on the Isle of Wight (22) based on interview and SPT reported peanut sensitization in 1.1% of 4-year-old children, 0.5% had an allergic reaction to peanut; relevance was, however, evaluated by questionnaire while oral challenges were not performed. So far, only one population-based study has evaluated the prevalence of peanut allergy in children confirmed by oral challenge (1). This study was performed by Grundy et al. (1) on the Isle of Wight and a point prevalence of peanut allergy on 1.5% was found. However, only 43% of the target population participated in the study and only open challenge was performed. The point prevalence in the present study was lower than reported by Grundy et al. (1). This can be caused by different exposure pattern to peanut in children in different countries and different study design.

In our study a weakness was that only 44% of the peanut sensitized participated in oral challenge. However, peanut sensitized school children reporting symptoms of peanut allergy were also among the children not participating in oral challenge. An overestimation of peanut allergy is therefore not expected.

Most peanut sensitized had atopic diseases, in agreement with previous studies (7, 22). Intermittent allergic rhinitis was seen in 58–74% of the school children with a positive CAP FEIA/SPT to peanut. Among school children sensitized to peanut in CAP FEIA nearly all (96%) had a concomitant reaction to grass pollen and in cases without clinically relevant peanut hyper sensitization the IgE class for grass was higher than for peanut. We therefore suggest a possible correlation between peanut and pollen (grass) sensitization. de Martino et al. (12) also suggested a possible cross-reaction between grass pollen and peanut by RAST and SPT and they verified the result by RAST inhibition.

We suggest that before a positive SPT or specific IgE measurement to peanut is considered clinically relevant in a patient, the case history should be evaluated together with

examination for pollen sensitization. Food challenge is still the 'gold standard' for diagnosing food allergies including suspected reaction to peanut.

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