

ORIGINAL ARTICLE

Can we predict severe reactions during peanut challenges in children?

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Abstract

Background: Limited and contrasting data are available about risk factors for severe reactions during double-blind, placebo-controlled food challenge (DBPCFC). Knowing these risk factors would help to improve safety precautions and choosing the best setting for challenge. We assessed whether we could determine predictors for positive and severe food challenge outcome (FCO) with regular available patient data in children suspected for peanut allergy.

Methods: A retrospective study in children referred for DBPCFC with peanut was performed during a 3-year period. Reactions during challenge were classified as mild/moderate (Sampson's grade 1–3) and severe (Sampson's grade 4–5). We performed uni- and multivariable logistic regression to determine predictors for positive and severe FCO.

Results: A group of 225 children with a median age of 6.7 (IQR 5.0–9.5) years were studied. In 109 (48%) children, food challenge outcome was positive and 24 (11%) children developed a severe reaction. The level of sIgE for peanut OR 1.14 (1.08–1.20), male gender OR 0.40 (0.20–0.81), having another food allergy OR 0.43 (0.20–0.88), were independently related to positive FCO. No significant differences were found between children with severe and non-severe FCO with respect to age, gender, asthma, sIgE, or previous reaction to peanut.

Conclusions: Although predictors of positive FCO could be identified, none of the studied risk factors could predict a severe reaction during peanut challenge. When challenging a child sensitized to peanut, clinicians should be prepared and equipped to handle any reaction in all cases.

Allergic reactions to food can vary from mild localized to severe generalized reactions with involvement of the respiratory and/or cardiovascular system (1). A double-blind, placebo-controlled food challenge (DBPCFC) is considered to be the gold standard for diagnosing food allergy (2). Severe reactions can occur during DBPCFC and are reported in 10–12% of patients challenged for peanut in previous studies (3–5). In common practice, a variety of patient-related factors, like previous severe reactions and age, is used to estimate the risk of a DBPCFC and to determine the precautions and the

setting of the challenge (6–9). Additionally, retrospective studies of community reactions showed that children with a fatal or severe reaction to food often had asthma (6, 7, 10, 11). However, the situation in daily life is different from that during DBPCFC, where the influence of other possible cofactors (e.g., active allergic disease, infections, alcohol, or exercise) is minimized (12). Moreover, when symptoms occur during DBPCFC, challenges are discontinued and treatment is given in an early stage. The evidence for using risk factors known from severe reactions in daily life to predict severity of food challenge outcome seems therefore limited and contradictory (3, 4, 13). Because peanut is one of the most common foods known for its capacity to elicit a severe life-threatening reaction (7), we investigated whether we could identify known risk factors for anaphylaxis in daily life as predictors for positive and severe FCO in children who underwent a DBPCFC for peanut.

Abbreviations

DBPCFC, Double Blind Placebo Controlled Food Challenge; OFC, Oral Food Challenges; FCO, Food Challenge Outcome; SPT, tSkin Prick Test; sIgE, Specific IgE; ED, Eliciting Dose; MD

Methods

Study design

Data were collected retrospectively from electronic patient records of oral food challenges, performed in the Wilhelmina Children's Hospital during a 3-year period. All children from urban and rural area with suspected peanut allergy who required DBPCFC were referred to this tertiary hospital. Children eligible for DBPCFC were more than 3 years old and suspect for having a peanut allergy by a previous allergic reaction to peanut and/or a raised sIgE and/or positive SPT. All children fulfilling these criteria were accepted for DBPCFC and included for this study, unless a previous reaction to peanut requiring hospitalization at an intensive care unit was reported. Data were obtained as part of regular patient care and were used in strictly anonymous form, according to the code of conduct for medical research approved by the hospital's Medical Ethical Committee.

Patient characteristics

Measurement of peanut-specific IgE (sIgE) was performed in all children within 1 year prior to DBPCFC, using Immuno CAP-technique (Phadia, Uppsala, Sweden), and IgE levels of ≥ 0.35 kU/l were considered positive. In a subset of children with available stored blood samples, sIgE for peanut component Ara h 2 was determined. Skin prick tests (SPT) were performed within 2 years prior to DBPCFC using a commercial peanut extract (ALK-Abelló, Nieuwegein, the Netherlands). For positive and negative control histamine dihydrochloride, 10 mg/ml and glycerol diluent were used, respectively. Mean diameter of peanut wheal size in millimeters was calculated from the average of the largest wheal diameter plus largest wheal diameter perpendicular to this. SPT was considered positive when the wheal was 3 mm greater in diameter than the negative control (14). Previous reactions to peanut were reported by the parents of the child and classified according to the Sampson's classification described below based on the most severe reaction observed. The presence of asthma, atopic dermatitis, allergic rhinitis, and other food allergies was determined in out-patient clinic consultations before DBPCFC. Asthma was defined as having a doctor's diagnose of asthma, together with the prescription of inhalant medication or inhaled corticosteroids (ATC code R03BA). Atopic dermatitis and allergic rhinitis were defined by doctor's diagnosis. Other food allergies were confirmed by a previous reported reaction combined with positive sensitization and/or a positive DBPCFC.

DBPCFC for peanut

Challenges were performed in a clinical setting equipped for resuscitation and monitoring of vital signs according to protocol. Only clinically stable children without recent infection, uncontrolled atopic disease or recent allergic reactions were eligible to start the challenge procedure. The DBPCFC protocol for peanut was described earlier by Flinterman et al. (15). The challenge was considered positive and terminated

when objective symptoms occurred or when consistent subjective symptoms occurred on at least three subsequent doses. The eliciting dose (ED) was determined as the lowest dose of peanut protein in mg eliciting objective allergic reaction. The cumulative dose (CD) was determined by the cumulative portion of peanut protein administered to the child in mg. Symptoms during challenge were graded after physical examination by one of the clinical experts and classified based on the most severe reaction observed in an organ system, according to the Sampson's classification (1). Severe food challenge outcome (FCO) was defined as a positive FCO with a severe respiratory and/or cardiovascular reaction of Sampson's grade 4 or 5 (severe stridor and/or dyspnea and/or wheezing and/or hypotension). Severe respiratory reactions were further classified into respiratory reactions with involvement of the upper airways (severe inspiratory stridor) and reactions with involvement of the lower airways (expiratory stridor or wheezing). Children with mild/moderate reactions were defined as having a reaction according Sampson's grade 1–3.

Statistical methods

Analyses were performed using SPSS for Windows (version 15.0 SPSS Inc., Chicago, IL, USA). A previous reaction to peanut in history was defined as a categorical variable with no previous ingestion/no previous reaction as reference category. Age was categorized in three groups (<6, 6–12, and >12 years). SPT and sIgE were used as continuous variables, and sIgE values >100 kU/l were deemed to be 101 kU/l. To avoid bias that might result from a complete case analysis, we imputed missing SPT data using multiple imputation (16). Univariate associations between candidate predictor variables and positive FCO and subsequently severe FCO were investigated using univariate logistic regression. Predictors that were univariately associated with the outcome (with a *p*-value <0.20) and/or clinically relevant were included in stepwise backward fashion selection in a multivariable logistic regression model to evaluate their independent value (*p*-value <0.05) in the prediction of positive FCO. Reliability (of goodness of fit) and calibration of the final model was estimated using the Hosmer–Lemeshow test. Prognostic capacity to differentiate between patients with and without positive FCO was estimated using the area under the receiver-operating characteristics curve (AUC). Food challenge characteristics in children with mild/moderate reactions and severe reactions were compared using Pearson's chi-squared test for categorical data and Mann–Whitney *U*-tests for nonparametric continuous data.

Results

A total of 225 DBPCFCs for peanut were performed and included for this study. Our study population consisted of predominantly boys (66%) and children had a median age of 6.7 (IQR 5.0–9.5) years. All children were sensitized for peanut by raised sIgE for peanut or positive SPT. In 88 (39%) children, stored blood samples were available to determine sIgE for peanut component Ara h 2. In 109 (48%) children, there was no known previous reaction to peanut in history. In

96 (43%) children, no previous known ingestion was reported and the other 13 (6%) children did consume peanut without developing acute symptoms in history. These children did, however, have a raised level of sIgE and were set on a prolonged peanut elimination diet for other reasons (e.g., eczema or symptoms after ingestion of an unknown allergen). Patient characteristics of the included study population are shown in Table 1.

Food challenge outcome

During challenge, 116 (52%) children appeared to be tolerant for peanut and 109 (48%) children developed symptoms of Sampson's grade 1–4 and had a positive FCO. No delayed reactions (after more than 4-h observation) occurred. ED, CD, symptoms, and treatment during challenge in children with positive FCO are shown in Table 2. Because asthma is thought to be an important risk factor for developing respiratory symptoms, we further compared asthmatic children with non-asthmatic children. In children with positive FCO, asthmatics did not report a severe respiratory reaction in history more often (29% compared with 22%, $p = 0.50$) and did not had a

reaction with involvement of the lower airways during challenge more often (12% compared with 15%, $p = 0.60$) than non-asthmatics (data not shown). Univariate analyses showed that six patient-related factors were significantly associated with FCO: male gender, having another food allergy, sIgE for peanut and sIgE for Ara h 2, wheal size of SPT, and a severe previous reaction in history. Based on clinical relevance and available data, male gender, asthma, the presence of another food allergy, sIgE for peanut, SPT, and the reaction to peanut in history were included in a multivariable model. The results show that the level of sIgE for peanut was positively associated with positive FCO (OR 1.14 (1.08–1.20), $p \ll 0.005$). Male gender (OR 0.40 (0.20–0.81), $p = 0.01$) and the presence of another food allergy (OR 0.43 (0.21–0.88), $p = 0.02$) were both negatively associated with a positive FCO. The reaction to peanut in history and SPT were not independently related to positive FCO after adjustment for the other factors. The final model showed good discrimination of children with positive and negative FCO with an AUC of 0.89 (0.84–0.93). However, calibration was poor, which is indicated by a significant Hosmer–Lemeshow test statistic of 34.99 (df = 8 and $p < 0.005$) (Table 3). The relation between

Table 1 Characteristics of included children with suspected peanut allergy and univariate relation with positive and severe FCO

Characteristic	All children n = 225	Positive FCO n = 109	Severe FCO n = 24	OR for positive FCO (95% CI)	p-value	OR for severe FCO (95% CI)	p-value
Median age (IQR, in yrs)	6.7 (5.0–9.5)	6.6 (4.8–9.0)	6.6 (4.8–7.7)	0.96 (0.89–1.04)	0.964	0.96 (0.84–1.09)	0.961
Age groups							
<6 years	121 (54)	63 (58)	14 (58)	Reference	–	Reference	–
6–12 years	74 (33)	32 (29)	7 (29)	0.70 (0.39–1.26)	0.701	0.80 (0.31–2.08)	0.799
>12 years	30 (13)	14 (13)	3 (13)	0.81 (0.36–1.80)	0.806	0.85 (0.23–3.17)	0.849
Male gender (%)	148 (66)	63 (58)	15 (63)	0.50 (0.29–0.87)	0.015*	0.85 (0.36–2.05)	0.720
Current other atopic diseases (%)							
Allergic rhinitis	96 (43)	47 (43)	9 (38)	1.04 (0.61–1.76)	0.894	1.03 (0.43–2.47)	0.444
Atopic dermatitis	184 (82)	88 (81)	10 (42)	0.87 (0.44–1.72)	0.873	0.85 (0.36–2.00)	0.835
Asthma (using ICS)	83 (37)	43 (39)	9 (38)	1.24 (0.72–2.13)	0.441	1.13 (0.36–3.50)	0.703
Asthma (using inhalants)	102 (45)	50 (46)	12 (50)	1.04 (0.62–1.76)	0.875	1.40 (0.60–3.25)	0.948
Any of above	217 (96)	103 (95)	24 (100)	0.66 (0.26–1.71)	0.392	1.02 (0.22–4.70)	0.983
Other food allergy	151 (67)	63 (58)	14 (58)	0.44 (0.25–0.77)	0.004*	0.65 (0.28–1.55)	0.335
SPT wheal (IQR, in mm)	8.50 (3.85–13.90)	11.60 (6.40–16.00)	10.10 (6.33–14.58)	1.14 (1.08–1.78)	0.000*	1.05 (0.95–1.15)	0.303
sIgE for peanut (IQR, in kU/l)	2.60 (0.60–19.20)	17.80 (4.35–86.0)	14.5 (2.7–39.0)	1.13 (1.08–1.19)	0.000*	1.00 (1.00–1.02)	0.123
sIgE for Ara h 2 (IQR, in kU/l)	n = 88 0.58 (0.07–6.46)	n = 43 6.48 (0.62–38.30)	n = 11 7.2 (2.1–41.0)	1.92 (1.27–2.91)	0.002*	1.02 (0.99–1.04)	0.097
Reaction to peanut in history (%)							
No symptoms/ingestion unknown	109 (48)	45 (41)	11 (46)	Reference	–	Reference	–
Previous non-severe reaction	76 (34)	40 (37)	7 (29)	1.58 (0.88–2.84)	0.370	0.90 (0.33–2.45)	–0.842
Previous severe reaction	40 (18)	24 (22)	6 (25)	2.13 (1.02–4.67)	0.044*	1.57 (0.54–4.58)	0.407

FCO, food challenge outcome; ICS, inhaled corticosteroids; IQR, inter-quartile range; OR, odds ratio; SPT, skin prick test.

Bold data were entered in the multivariate logistic regression model.

*Significantly related to the outcome, $p < 0.05$.

Table 2 Reaction thresholds, symptoms, and treatment during challenge in children with positive, mild/moderate, and severe FCO

Characteristic	Positive FCO n = 109	Mild/moderate FCO n = 85	Severe FCO n = 24	p-value
Median ED (IQR, in mg peanut protein)	150 (50–500)	150 (50–500)	150 (50–1500)	0.65
Median CD (IQR, in mg peanut protein)	706 (206–2206)	706 (206–2206)	706 (56–2206)	0.91
Symptoms during challenge (%)*				
Skin	50 (46)	41 (48)	9 (38)	0.35
Grade 1 (localized pruritus)	15 (14)	13 (15)	2 (8)	
Grade 2 (generalized pruritus)	35 (32)	28 (33)	7 (29)	
Gastro-intestinal tract	93 (85)	75 (88)	18 (75)	0.12
Grade 1 (OAS)	14 (13)	11 (13)	3 (13)	
Grade 2 (+ nausea/emesis)	71 (65)	58 (68)	13 (54)	
Grade 3 (+ repetitive vomiting)	6 (6)	5 (6)	1 (4)	
Grade 4 (+ diarrhea)	2 (2)	1 (1)	1 (4)	
Respiratory tract	67 (62)	44 (52)	23 (96)	0.00
Grade 2 (nasal congestion/sneezing)	32 (29)	32 (38)	–	
Grade 3 (rhinorrhea, throat pruritus/tightness)	12 (11)	12 (14)	–	
Grade 4	23 (21)	–	23 (96)	
Upper airways (inspiratory stridor)	8 (7)	–	8 (33)	
Lower airways (wheezing, expiratory stridor)	15 (14)	–	15 (63)	
Cardiovascular (grade 4, hypotension)	1 (1)	–	1 (4)	0.22
Neurological	2 (2)	1 (1)	1 (4)	0.34
Grade 2 (change in activity level)	1 (1)	–	1 (4)	
Grade 3 (+ anxiety)	1 (1)	1 (1)	–	
>2 organ systems involved	88 (81)	66 (78)	22 (92)	0.15
Treatment during challenge (%)				
AH and CS	84 (77)	84 (1)	–	–
+ Inhalation therapy	9 (8)	–	9 (38)	–
+ Adrenaline i.m./i.v.	16 (15)	1 (1)	15 (63)	–

CD, cumulative dose; ED, eliciting dose; FCO, food challenge outcome; IQR, interquartile range.

*Symptoms during challenges were graded according to Sampson et al. (1).

the presence of another food allergy and positive FCO was further explored with a subgroup analysis. No significant differences between children with and without another food allergy with respect to other patient characteristics, SPT results, level of sIgE, correlation between SPT and sIgE for peanut, ED, or CD were found. In this study, 109 children without a previous reaction to peanut were included. Adding the presence of a previous reaction to the final model with gender, other food allergy and sIgE, however, did not change the estimates of the model which indicates that the inclusion of children without a previous reaction to peanut did not interfere with our results. We also performed multivariable analysis in the subgroup of 88 children with available Ara h 2 results. In a model with male gender and the presence of other food allergy, there was a clear and strong association of Ara h 2 with positive FCO (OR 3.52 (1.71–7.29), $p \ll 0.005$). This model also showed good discrimination of children with positive and negative FCO with an AUC of 0.97 (0.93–1.00) and was well calibrated with a non-significant Hosmer–Lemeshow test statistic of 6.30 (df = 7, $p = 0.51$) (Table 3).

Severe food challenge outcome

Twenty-four children (11%) developed a severe reaction during DBPCFC and had a severe FCO. In 92% of these children,

more than two organ systems were involved in the allergic reaction during challenge. The majority of children with severe FCO had severe respiratory symptoms of Sampson's grade 4. Upper respiratory symptoms with severe throat tightness occurred in eight children and wheezing due to lower airway involvement in 15 children. Only one child developed a severe drop in blood pressure. The occurrence of skin symptoms, gastro-intestinal symptoms, and neurologic symptoms was comparable between children with mild/moderate FCO and children with severe FCO. In 9 (38%) children with severe FCO, treatment with inhalants was indicated as lower respiratory symptoms were the main manifestation of anaphylaxis; moreover, 15 (63%) children received adrenaline. The ED (median [IQR]) was not significantly different between children with mild/moderate (150[50–500] mg) and severe (150[50–1500] mg) FCO, $p = 0.65$. Moreover, there was no difference in the CD of peanut ingested (median [IQR]) between children with mild/moderate and severe FCO (706[206–2206] mg and 706[56–2206] mg, $p = 0.91$) (Table 2).

Univariate analyses did not show significant associations of any of the candidate predictors with severe FCO (Table 1). In the subgroup of 88 children with available Ara h 2 results, sIgE for Ara h 2 was also not significantly related to severe FCO, OR 1.02 (0.99–1.04), $p = 0.10$. Due to the relatively low incidence of severe FCO, only the most clinical relevant

Table 3 Multivariable analyses of predictors for children with positive or severe FCO

Predictor	Adjusted OR for positive FCO (95% CI)	p-value	Adjusted OR for positive FCO (95% CI) *	p-value	Adjusted OR for severe FCO (95% CI)	p-value
Male gender (%)	0.40 (0.20–0.81)	0.011	0.03 (0.003–0.19)	0.000	–	–
Other food allergy	0.43 (0.21–0.88)	0.021	0.25 (0.05–1.17)	0.077	–	–
sIgE for peanut (kU/l)	1.14 (1.08–1.20)	0.000	–	–	1.00 (0.99–1.02)	0.104
sIgE for Ara h 2 (kU/l)	–	–	3.52 (1.71–7.29)	0.001	–	–
Reaction to peanut in history (%)						
No reaction/no known ingestion					Reference	–
Previous non-severe reaction					0.80 (0.29–2.21)	0.661
Previous severe reaction					1.49 (0.50–4.42)	0.469
ROC area (95% CI)	0.89 (0.84–0.93)		0.97 (0.93–1.00)			
Hosmer–Lemeshow (chi-squared statistic)	34.99 (df = 8)	0.000	6.30 (df = 7)	0.506		

FCO, food challenge outcome; OR, odds ratio; ROC, receiver under the operator curve.

*Subgroup of children with known sIgE to Ara h 2, n = 88.

predictors (asthma, sIgE for peanut, and reaction to peanut in history) were entered in a multivariate model. None of the predictors were significantly associated with severe FCO (Table 3).

Discussion

The main goal of food challenges is to confirm or exclude the presence of food allergy under safe conditions. However, severe reactions during challenges do occur; in our study, 11% of peanut challenged children had severe FCO, which is comparable with previous published results (3–5). Our results confirm that there are patient-related factors associated with positive food challenge outcome, but no independent risk factors for severe FCO could be determined.

Some limitations have to be considered when interpreting the results of this study. The results of this study are based on retrospective data of food challenges. For the presence of other atopic diseases, we had to rely on doctor's diagnosis; nevertheless, this is conform daily practice. We also had no complete data on SPT and Ara h 2 results. However, we think imputation of SPT values leads to unbiased complete results. Regarding to our finding that Ara h 2 is predictive for positive FCO, but not significantly related to severe FCO, we think more research in prospective setting is necessary to confirm this in an unselected study population. In this study, food challenges were performed in children referred to a tertiary setting which could have led to selection bias. However, in our hospital, all children suspected for peanut allergy (including children without a previous reaction and children with a previous severe reaction) were challenged. Because only a few children with a life treating in history were excluded, we think our study involves the complete spectrum of peanut allergy.

Improving diagnostics in food allergy is a topic leading to much discussion in the literature, and daily practice and several prediction rules to predict FCO and reduce the need for oral

food challenges have been published (17, 18). In this study, the level of sIgE and not SPT reactivity appeared to be an independent predictor for positive FCO. Earlier studies showed an AUC of 0.79–0.86 for SPT and 0.77–0.87 for sIgE to peanut, respectively (19–22). However, as is stated before (23, 24), cross-reactivity with other allergens (e.g., grass pollen or other foods) can interfere with levels of sIgE and reactivity of SPT, which can explain the relatively low predictive capacity of both measures. In the near future, promising results regarding component resolved diagnostics provide opportunities to improve the diagnostic capacity of sIgE and SPT in predicting positive FCO (25). We did not expect to find that male gender was related to negative FCO due to the gender-specific prevalence of food allergy before puberty, which is higher in boys than in girls (26). However, previous studies in young children with respiratory symptoms showed that there are gender differences in healthcare utilization by parents and prescription of medication by physicians in favor of boys (27, 28). It is therefore not beyond possibility that clinicians tend to perform DBPCFCs more easily in boys. Although peanut sensitization is thought to be more present in children with other atopic disorders including food allergies (29), having another food allergy was negatively associated with positive FCO in our study. It could be that there is a higher proportion of children with unjustified suspected peanut allergy among children with other food allergies compared with children without any other (suspected) food allergy in our study.

In this study, important risk factors for anaphylaxis in daily life as having asthma, the level of sIgE, and severe reaction in history were not independently associated with severe FCO. Severity of allergic reactions during challenge may depend on the interaction between several host and event-related factors (30). Of the event-related factors, ED and the amount of food ingested during challenge can be associated with the severity of reaction during challenge (31). In our study, no differences were found between children with mild/moderate and severe FCO regarding to the CD of peanut given, indicating that

children with mild/moderate FCO were not 'prevented' from developing a severe reaction. Our results indicate that previous reactions reported by parents cannot be used to predict severity of food challenge outcome, which is supported by others (4, 13). This could be due to an inaccuracy in the description of allergic symptoms by the parents, but can also be due to the different circumstances and absence of cofactors during challenge, which can aggravate reactions in daily life. Our results regarding to the value of sIgE for peanut and SPT in predicting severe FCO are in contrast with two other studies who did found a correlation between the level of sIgE for peanut and anaphylaxis during challenge (13, 32). However, the suggested cutoff values of both studies have not been validated in other less selected populations. Moreover, others confirm our results that levels of sIgE for peanut cannot be used to estimate the risk of anaphylaxis during challenge (3, 19, 20, 33, 34). Studies investigating accidental anaphylaxis to food indicate that children with fatal or severe reactions to food in daily life often have asthma, suggesting this to be an important risk factor for severe reactions (35–37). As has been shown before (3, 13), our results point out that we cannot generalize these findings to the setting of food challenges. Children eligible for challenge have clinical stable asthma without recent exacerbations in contrast with possible uncontrolled circumstances during severe reactions in daily life (38, 39). Our results also indicate that lower respiratory tract symptoms are relatively

rare in children with positive FCO (14%), but if they occur, this is both in children with and without (stable) asthma.

In conclusion, this study shows that clinical information gathered before food challenge can be used to predict positive FCO; in contrast, we were unable to identify children with suspected peanut allergy as high or low risk of severe FCO. To extrapolate these results to daily practice and develop a well-calibrated prediction model for positive and severe FCO, internal and external validation in a larger study population is necessary. Until more extensive and prospective studies are conducted, possible risk factors known from daily life studies cannot guide the eligibility of a patient for food challenges or the setting and safety precautions taken. Clinicians performing peanut challenges in sensitized patients should be prepared and well equipped for treatment of a severe reaction in all cases.

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Conflict of interest

All authors certify that there is no conflict of interest and there is no disclosure of financial interest.

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