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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

Peanut avoidance and peanut allergy diagnosis in siblings of peanut allergic children

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Summary

Background Studies suggest that siblings of children with peanut allergy (PNA) have a higher prevalence of PNA than the general population.

Objectives The Canadian Peanut Allergy Registry was used to assess the percentage of siblings of registered index PNA children who were 1) never exposed to peanut or 2) reportedly diagnosed with PNA by a physician without either a history of allergic reaction or a confirmatory testing. Sociodemographic and clinical factors that may be associated with either outcome were evaluated.

Methods Parents completed a questionnaire on siblings' sociodemographic characteristics, exposure and reaction to peanut, confirmatory tests performed and whether PNA had been diagnosed.

Results Of 932 Registry families, 748 families responded, representing 922 siblings. 13.6% of siblings had never been exposed to peanut, 70.4% (n = 88) of which were born after the index child. Almost 9% of siblings (80) were reported as PNA, but almost half of this group had no history of an allergic reaction to peanut, including five children who also had no testing to confirm PNA. Of these 5, 4 were born after PNA diagnosis in the index child. In a multivariate regression analysis for siblings at least 3 years old, those born after PNA diagnosis in the index child were more likely to have never been exposed to peanut. In a univariate analysis, siblings born after the diagnosis of PNA in the index child were more likely to be diagnosed with PNA without supportive history or confirmatory testing.

Conclusions and Clinical Relevance These data estimate that more than 10% of siblings of PNA patients will avoid peanut and that siblings born after the diagnosis of PNA in an index child are more likely to have never been exposed. Educational programs and guidelines that caution against unnecessary avoidance are required.

Keywords diagnostic testing, food allergy, peanut allergy, siblings

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Introduction

Siblings of children with peanut allergy (PNA) are reported to have a higher prevalence of PNA than the general population [1, 2]. This likely results from both genetic and environmental influences, but may also reflect incorrect diagnosis in siblings because of less rigorous usage of confirmatory tests. Due to the perception of the inherent increased risk in siblings of PNA children, parents may presume the sibling is also allergic and be less likely to seek medical attention; similarly, physicians may believe that referral or confirmatory testing is unwarranted as PNA is highly likely. However, while previous studies suggest an increased risk for peanut allergy in siblings [1, 3], more recent studies yield less conclusive results [4]. Further, increasing evidence

shows that unnecessary avoidance – because of a fear of an unconfirmed PNA – may actually increase the risk of developing PNA [5–7].

The Peanut Allergy Registry (PAR) is a Canadian database of individuals with PNA. We evaluated the percentage of siblings of registry participants who were 1) never exposed to peanut or 2) reportedly diagnosed with PNA by a physician without either a history of an allergic reaction or confirmatory testing. In addition, we assessed the effect of the clinical characteristics of PNA index children, as well as sociodemographic factors of the siblings and family, on the outcomes listed above.

Methods

Study design

A questionnaire was distributed to all PAR families between September and December 2012. The Canadian PAR includes children with physician-confirmed PNA recruited from the Montreal's Children Hospital between 2000 and 2012 and Canadian food allergy advocacy organizations, including Anaphylaxis Canada, Association Québécoise des Allergies Alimentaires, and the Allergy and Asthma Information Association, between 2006 and 2012. Participants in the PAR are considered to have PNA based on the clinical characteristics of the reaction to peanut and results of confirmatory tests obtained through chart review or from the treating allergist. Children were considered to be allergic to peanut if they fulfilled the following specific criteria:

1 A convincing clinical history of an allergic reaction to peanut AND a positive skin prick test (SPT) to peanut OR a peanut-specific IgE (PN-IgE) level of at least 0.35 kU/L

or

2 No clinical history or uncertain history of an allergic reaction to peanut and EITHER

i) a positive SPT to peanut AND a PN-IgE level of at least 15 kU/L

OR

ii) a positive oral challenge to peanut [8–11].

Data were collected on the number of siblings, sex, age and birth order as well as siblings' exposure to peanut, allergic reaction to peanut, results of clinical testing (SPT, PN-IgE, or oral challenge) and parent report of PNA diagnosis by a physician. Data already existed in the PAR on demographic characteristics of the family and index child, including site of recruitment (Montreal Children's Hospital vs. food allergy advocacy organizations), province of residence, parental educational level and marital status, and sex, age, severity of most severe reaction and presence of co-morbidities [8].

The study was approved by the McGill University Health Centre Research Ethics Board.

Statistical analysis

Univariate and multivariate logistic regression models were used to estimate the associations between characteristics of the index child/siblings/family and the following outcomes in siblings:

i) No history of peanut exposure among a) all siblings and b) those 3 years and above,
ii) Reported as having physician-diagnosed PNA with no history of clinical reaction or positive diagnostic tests among all siblings reported with physician-diagnosed PNA.

Predictors included age, sex of the index child, site of recruitment, co-morbidities (asthma, eczema, hay fever and other food allergies), and severity of allergic reaction in index child (mild, moderate or severe as previously defined) [9]; age of siblings at the time of PNA diagnosis in index child (younger or older than index child); siblings' sex, province of residence, sibship size, parental education level (completed college or university) and marital status of household respondent (single parent/living with partner/married). A Bayesian hierarchical model was fit using WinBUGS (Version 1.4.3, Cambridge, UK) to account for potential clustering effects within families.

Results

Patients and characteristics

All PAR families with at least one case of PNA were surveyed ($n = 932$) and 748 (80.3%) families responded. Demographic and clinical characteristics of the index child and sociodemographic characteristics of the family were largely comparable between respondents and non-respondents; however, among respondents, a slightly higher percentage reported mild reactions (Table 1).

Among the participating families, a total of 922 siblings were reported (Table 2). The median age was 11.7 years, the majority were males, and 56.9% were younger than the index child; 94.5% were older than 3 years of age at the time of the survey.

Siblings never exposed to peanut

Of the entire sibling group ($n = 922$), 764 had been exposed, 33 were uncertain whether they had been exposed and 125 [13.6% (95% CI, 11.4%, 16.0%)] had never been exposed to peanut. Among those never exposed, the majority (88 of 125) were born after the diagnosis of peanut allergy in the index child. Of the

Table 1. Registry respondents vs. non-respondents

Variable	Respondents (N = 748)	Non-respondents (N = 184)
Age in years of index case at the time of survey (median IQR)	12.0 (9.07, 15.20)	12.8 (9.7, 17.3)
Sex of index case (% males)	65.9	58.1
*Severity of most severe reaction of index case		
Mild (%)	23.1	15.5
Mod (%)	50.8	47.5
Severe (%)	26.1	31.1
Mother's education, college and above (%)	73.3	65.4
Father's education, college and above (%)	71.4	62.6
Single family (%)	6.5	9.2

*5.9% of non-respondent registry participants were diagnosed without a history of reaction according to PN-IgE cut-off levels published in the medical literature.

Table 2. Characteristics of 922 siblings

Variable	% (95% CI)
Sibship size	
2	50.1 (46.8, 53.4)
3	37.4 (34.3, 40.6)
4	8.7 (7.0, 10.7)
5	2.2 (1.4, 3.3)
6	1.6 (0.9, 2.7)
% of sibling ≥3 years at time of survey (n = 871)	94.5 (92.7, 95.8)
% of siblings ≥5 years at time of survey (n = 806)	87.4 (85.1, 89.5)
Age in years of siblings (median, IQR)	11.7 (7.4, 16.3)
Sex (males)	52.1 (48.8, 55.3)
Younger than index PNA patient	56.9 (53.7, 60.2)
Ever exposed to peanut?	
Yes (n = 764)	82.9 (80.2, 85.2)
Not sure (n = 33)	3.6 (2.5, 5.0)
Never (n = 125)	13.6 (11.4, 16.0)
• and born after PNA diagnosis in index patient (n = 88 of 922)	9.5 (7.8, 11.7)
Never exposed and at least 3 years old (n = 93)	10.7 (8.7, 13.0)
• and born after PNA diagnosis in index patient (n = 58 of 922)	6.7 (5.1, 8.6)
Never exposed among those at least 5 years old (n = 67)	8.3 (6.5, 10.8)
• and born after PNA diagnosis in index patient (n = 43 of 922)	5.3 (3.9, 7.2)
Parent-reported physician diagnosis of PNA (n = 80)	8.7 (7.0, 10.7)
• among 125 never exposed to peanut (n = 21 of 125)	16.8 (10.9, 24.8)

125 who had never been exposed, 21 were reported by their parents to have a PNA. When the entire group (922) was limited to 871 siblings that were at least 3 years of age, 93 [10.7% (95% CI, 8.7%, 13.0%)] had never been exposed to peanut (Table 2) and the majority of those never exposed (58 of 93) were born after the diagnosis of peanut allergy in the index child.

Siblings reported as PNA

Of the sibling group (n = 922), 80 were reported by parents to be diagnosed by a physician as having PNA [8.7% (95% CI, 7.0, 10.7)]. Among these 80, the median age was 12.3 years and the majority were males (Table 3); 41 (51.3%) had reacted to peanut; in five cases (6.3%), parents were not sure whether the child had a reaction and 34 (42.5%) had never reacted. Among the 34, 29 had a positive confirmatory test, and five were diagnosed as allergic without a history of reaction and without confirmatory testing (*i.e.* tests did not support the diagnosis or were not performed at all).

Factors predicting peanut exposure and PNA diagnosis

Never exposed to peanut. In the univariate analysis examining the association between no history of peanut exposure and a variety of covariates, when all (922) siblings are included, siblings born after the diagnosis of PNA in the index child were more likely to have never been exposed to peanut (OR = 6.2, 95% CI, 4.1, 9.4). However, in the multivariate model including all siblings, wide CIs precluded a conclusive association. Increasing age was associated with lower odds for peanut avoidance, that is for each increase of 1 year in age, there is decreased likelihood (OR = 0.7, 95% CI, 0.6, 0.8) of peanut avoidance.

In the multivariate analysis including only siblings 3 years or older, siblings born after the diagnosis of PNA in the index child were more likely to have never been exposed to peanut (OR = 2.5, 95% CI, 1.1, 6.9).

PNA diagnosis. Of the 34 children reported with PNA who never had a clinical reaction, 7 (20.6%) had only a positive skin test, 20 had both a positive skin test and PN-IgE levels reported by parents as positive (58.8%), and two had a positive oral challenge to peanut (5.9%). The remaining five children were diagnosed with no history of clinical reaction and no confirmatory tests. Given the absence of reaction and (in five cases) added absence of confirmatory tests, it is possible that a substantial number were incorrectly diagnosed with PNA. We therefore assessed factors associated with the diagnosis of PNA in the dual absence of clinical reaction and confirmatory tests among the 80 siblings reportedly diagnosed with PNA.

In univariate analysis, siblings born after PNA diagnosis in the index child were more likely to have been

Table 3. Demographics and clinical characteristics of 80 sibling participants reported with peanut allergy

Variable	% (95% CI)
Age in years (median, IQR)	12.3 (8.4, 14.7)
Age ≥3 years	96.3 (88.7, 99.0)
Sex (males)	58.8 (47.2, 69.5)
Ever reacted to peanut (n = 41)	51.3 (39.9, 62.5)
Not sure if reacted to peanut (n = 5)	6.3 (2.3, 14.6)
Diagnosed with PNA without a history of reaction (n = 34):	42.5 (31.7, 54.0)
With +SPT or +PN-IgE or +Challenge (n = 29)	
Had only SPT: (7 of 34)	20.6 (9.3, 38.4)
Had SPT and IgE: (20 of 34)	58.8 (40.8, 74.9)
Had a FC: (2 of 34)	5.9 (1.0, 21.1)
Without +SPT or +PN-IgE or +Challenge (n = 5) and born after diagnosis of PNA in index case (4 of 5)	80 (29.9, 98.4)

diagnosed as PNA without a supportive history of clinical reaction or confirmatory tests (OR, 12.7; 95% CI, 1.3, 120.7). However, in a multivariate model, conclusive association was precluded due to wide confidence intervals. Associations with other predictors were also inconclusive due to wide confidence intervals.

Discussion

We have surveyed the largest reported group of siblings of children with PNA and report a trend of greater peanut avoidance and potential overdiagnosis of PNA in siblings born after the diagnosis of PNA in an index child.

Among siblings aged 3 years or older, those born after PNA diagnosis in the index child were more likely to have never been exposed to peanut. A previous study we conducted in Montreal school children (aged 5 – 9 years) suggested that only 4.5% were never exposed to peanut [12]. In contrast, in this study, 10.7% of siblings of children with PNA that were 3 years or older at the time of the survey were never exposed to peanut [difference: 6.2% (95% CI, 4.0%, 8.4%)] and when restricting to siblings that were at least 5 years old, 8.3% were never exposed [difference: 3.8% (1.8%, 5.9%)].

Such peanut avoidance may be explained by previous studies suggesting that age of introduction of allergenic foods is often later in atopic vs. non-atopic families as delayed introduction was once thought to decrease the likelihood of allergy [13]. This dietary manipulation may, however, result in reverse causation [14], whereby delaying the oral ingestion of peanut in siblings may in fact increase the likelihood of peanut allergy, as has been discussed in recent studies on the epidemiology of peanut allergy [5–7].

While past recommendations stated that children under the age of 3 years should not eat peanut [15], these recommendations were retracted in 2008 given emerging literature suggesting that this practice is not beneficial for primary prevention of food allergy [11, 12]. It is possible that this older recommendation was still followed by some families. However, the association between sibling birth after diagnosis of the index child and peanut avoidance was even stronger when the analysis was restricted to siblings 3 years and older. Hence, it is likely that anxiety related to having a previous child with PNA affects the decision to introduce peanut even beyond the previously recommended time interval [16]. While some families of children with PNA may purge their homes of peanut, as per guidelines that advise strict avoidance of peanut for the affected child [17], the impact of this practice on unexposed siblings is not yet understood and may, in fact, have a negative effect on the development of tolerance [5–7].

The prevalence of parent-reported physician PNA diagnosis among this sibling group was 8.7% (95% CI, 7.0%, 10.7%), comparable to other published studies of smaller groups that have ranged from 6.9% (95% CI, 5.1%, 9.3%) to 8.5% (95% CI, 2.8%, 21.3%) [1, 3]. Our higher percentage of parent-reported PNA in siblings may reflect those siblings who were diagnosed based only on evidence of sensitization to peanut (skin or blood testing) or who were presumed by parents or physicians to have PNA, but had neither an allergic reaction nor supportive testing.

This phenomenon has not been previously reported and may reflect behaviours and attitudes derived from the parental anxiety associated with a PNA diagnosis in a child [18] and the desire to protect other children in the family from a potential allergic reaction to peanut. Parents may prefer to minimize the risk and anxiety induced by allergic reactions in children that are known to have reacted and in those who might react to peanut by avoiding them altogether. Furthermore, in almost 50% of siblings, the reported PNA diagnosis was in the absence of a history of clinical reaction – either with or even without (in five cases) confirmatory testing. Basing the diagnosis of PNA on confirmatory tests alone may be misleading. Different positive predictive values for threshold size of peanut skin tests and levels of PN-IgE have been published [10, 19, 20], and it is suggested that a skin test diameter of at least 13 mm [19] may be required to establish the diagnosis of peanut allergy in children who were never exposed to peanut. Given such uncertainty, the routine use of these confirmatory tests in individuals never exposed to peanut should not be encouraged and may not be adequate as a sole criterion for PNA diagnosis.

Guidelines and educational programs specifically cautioning against unnecessary peanut avoidance in

siblings should be distributed to families of PNA children until the results of studies determining the optimal age of peanut introduction are available. Recently, the National Institution of Allergy and Infectious Disease (NIAID) and the Canadian Society of Allergy and Clinical Immunology (CSACI) each released statements, affirming that there is no evidence that delaying the introduction of any specific food beyond 6 months of age helps to prevent allergy – even in families with an index child with PNA. The statements discourage routine pre-exposure screening for food allergy using skin testing or specific IgE blood testing; for reluctant families, including those having older siblings with food allergy, it is suggested that a treating allergist supervises oral food challenges as an alternative to these tests [17, 21, 22].

The need to prevent accidental exposure to the PNA sibling begs the question of how exactly a family may accommodate timely and early introduction of peanut to younger siblings. This is a task that requires some attention and may include designated peanut vs. peanut-free zones of a kitchen or home. We suggest that families must be encouraged to take on this challenge, with guidance from their physicians and food allergy advocacy organizations, in lieu of presuming younger siblings to be PNA without appropriate confirmation.

Our study is limited in that we relied on parent reports of sibling PNA diagnosis, without obtaining copies of test results or allergy consultation reports. In addition, the PAR considers registered index patients with a PN-sIgE >15 KU/L reported with PNA by their physicians to be peanut allergic, regardless of a clinical history of allergic reaction to peanut, and this group represents less than 10% of the index patients. It is possible that this group is asymptomatically sensitized and peanut tolerant, although the 15 KU/L is a widely accepted threshold [23]. However, the inclusion of such index patients still tests the hypotheses that siblings of children *perceived* as PN allergic by their parents are more likely to have never been exposed to peanut or presumptively, incorrectly diagnosed as PNA themselves. Another potential limitation is that the PAR does not have equal representation from all areas of Canada, which may create a referral bias.

In conclusion, our findings suggest that parents of PNA children may be delaying or preventing altogether the oral introduction of peanut to younger siblings and that some of these siblings may be given poorly established diagnoses of PNA themselves. Siblings born after vs. before the diagnosis of PNA in the index child are more likely to have never been exposed to peanut.

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Conflict of interests

The authors declare no conflict of interest.

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Authors' contributions

Elana Lavine, Ann Clarke, Reza Alizadehfar, Yuka Asai and Moshe Ben-Shoshan provided substantial contributions to conception and design, analysis and interpretation of data. Elana Lavine and Ann Clarke drafted the article. Ann Clarke, Lawrence Joseph, Reza Alizadehfar, Yuka Asai, Edmond Chan, Laurie Harada, Mary Allen and Moshe Ben-Shoshan acquired data. Lawrence Joseph provided substantial contributions to conception and design, statistical analysis and interpretation of data. Gregory Shand provided substantial contributions to conception and design and interpretation of data. All authors revised the manuscript critically for important intellectual content and approved the final version to be published.

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