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Article type : Letter to the Editor

Title

Development of peanut allergy despite early introduction: A real-world case series in the United States.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PAI.13226](#)

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Funding: No funding was received for this work.

Conflicts of interest:

Dr Anagnostou is the PI of peanut oral immunotherapy trials and receives Institutional funding from Aimmune Therapeutics.

Dr Anvari is the PI for patch immunotherapy peanut studies and receives Institutional funding from DBV Technologies.

Dr James reports no conflicts of interest.

Word Count: 1417 (max: 1200)

To the Editor:

Peanut allergy rates have nearly tripled in the last decade ^{1 2 3}. Initial guidelines, promoting avoidance of allergenic foods in infants had no effect on the rising prevalence of food allergies and the recommendations were reversed based on new evidence ⁴. The LEAP (Learning Early About Peanut Allergy) trial confirmed that early peanut introduction significantly reduces the risk of developing peanut allergy in high-risk infants (defined as those with severe eczema and/or egg allergy) ⁵. Following these findings, the NIAID published a consensus report encouraging early introduction of peanut in infants depending on individual risk, testing results and family preferences ⁶.

These guidelines are currently followed by many allergists and it is assumed that after a negative peanut challenge and initial successful introduction, there should be no further concerns regarding peanut allergy. Optimal frequency and dosing of peanut consumption has not been fully

investigated, but regular consumption is usually defined as eating 6-7 grams of peanut over 3 or more feedings, according to the NIAID ⁶.

We report a series of infant cases from our center, who, despite early introduction and initial tolerance to peanut, subsequently developed IgE-mediated peanut allergy or peanut-triggered FPIES (Table I). IRB approval was obtained for this study.

Patient 1 is a 19-month-old male who introduced peanut at 7 months of age and tolerated it well until 11 months with regular exposure. At 12 months of age, after ingestion of a peanut butter sandwich, he immediately developed significant eye swelling and facial angioedema. He was taken to the ED and given oral diphenhydramine with resolution of symptoms. Peanut specific IgE level was elevated at 5.41kU/L. Peanut skin prick test (SPT) was positive with a 7mm wheal.

Patient 2 is a 13-month-old female with negative peanut SPT and oral challenge at 12 months of age, and subsequent tolerance of peanut in the form of 3-4 tablespoons of peanut butter every week. At 13-months of age, she developed widespread hives immediately after consumption of peanut butter. Peanut SPT was found positive with a 12mm wheal.

Patient 3 is a 12-month-old male introduced to peanut at 6-months of age. He had been tolerating peanut butter, but consumption was irregular. At 12-months of age, peanut ingestion was accompanied by generalized urticaria on three separate occasions. Peanut specific IgE at that time was reported as 1.41 kU/L, Ara h 2 was 0.25kU/L and in conjunction with the clinical history a diagnosis of peanut allergy was made. At 2 years of age, he had another episode of hives and facial swelling after eating a chocolate chip granola bar manufactured in a factory handling peanuts. He has avoided peanut since the age of 1 year.

Patient 4 is an 11-month-old male with history of eczema and concerns for IgE-mediated food allergy to milk and egg. He underwent a peanut butter oral challenge at 6-months of age and passed. He was eating peanut butter once weekly for about 1 month. The family discontinued peanut butter ingestion after 1 month of tolerance for unknown reasons and tried to reintroduce again at 8-

months of age. After 1/8tsp, the patient immediately developed hives on his face and was treated with diphenhydramine. Peanut specific IgE was 1.96kU/L.

Patient 5 is a 15-month-old male who previously tolerated irregular consumption of peanut butter without reaction. At 15-months he developed bilateral eyelid swelling, nasal drainage, and hoarseness within 30 minutes of reported contact with peanut butter (ingestion was suspected, but unconfirmed). He was given diphenhydramine at home and was taken to Urgent Care. By 30 minutes, his symptoms had completely resolved without any further intervention. At 17-months SPT showed a 13mm wheal for peanut.

Patient 6 is an 11-month-old female with history of eczema and concern for cow's milk protein proctocolitis (blood and mucus in stool) initially seen at 3-months of age. Mom eliminated dairy, tree nuts, peanut, shellfish, fish, egg and soy from her diet, while breastfeeding, with resolution of the infant's symptoms. At 6-months of age peanut SPT was negative and she passed a peanut butter oral challenge, subsequently consuming peanut at least three times a week for two weeks. At 7-months of age, she presented to the ED with persistent vomiting and cough approximately 2.5 hours after the 6th home peanut butter exposure. No angioedema or hives were noted and epinephrine was not given. One week later, peanut butter was reintroduced at home gradually over 1.5 hours. Twenty minutes after the final dose, she developed vomiting and repetitive cough. She was given diphenhydramine and epinephrine and was observed in the ED for 4 hours before discharge. Peanut SPT and IgE testing were repeated and remained negative. A diagnosis of FPIES to peanut was made.

Patient 7 is a 7-month old female with history of eczema and initial negative peanut SPT who passed an oral challenge. Following this, she ingested peanut daily diluted with breast milk for 2 weeks. The patient developed a viral URI and discontinued peanut butter ingestion for 2-3 days. On peanut butter reintroduction, mom reported that the infant developed profuse vomiting 6 hours after ingestion. Introduction was repeated 5 days later, and the patient was again noted to have profuse vomiting 2 hours after ingestion, suggestive of an FPIES reaction. The family deferred peanut IgE and SPT following the reaction and have been avoiding peanut since.

We describe 7 different infants with initial successful peanut introduction, but subsequent development of allergic reactions. In 4 cases, peanut consumption was regular and in adequate amounts (based on current guidelines). In 3 cases, peanut consumption was irregular with reduced frequency than currently recommended. Five of our patients developed IgE-mediated peanut allergy, whereas two developed FPIES to peanut. Peanut was generally tolerated for 1-6 months prior to the development of allergy.

To our knowledge we are the first group to describe five cases of IgE-mediated reactions to peanut following successful initial introduction and tolerance, in a real-world clinic setting. In the research setting, the LEAP study investigators reported a small number of infants developing peanut allergy despite regular early introduction ⁵. Our two cases of peanut-triggered FPIES reinforce previous findings by other investigators reporting three similar cases ⁷.

While not regularly reported, it is not uncommon to see recurrences of peanut allergy. Fleischer et al report recurrence of peanut allergy in 3 of 15 patients who consumed peanut infrequently or in limited amounts, compared with no recurrences in the 23 patients who ate peanut frequently, showing a recurrence rate of 7.9% ⁸. The investigators conclude that children who outgrow peanut allergy are at risk for recurrence, and this risk is significantly higher for patients who continue largely to avoid peanut after resolution of their allergy ⁸.

It is also possible that these are events occurring due to children being exposed to peanut earlier in life as a result of the early introduction guidelines. A recent publication has shown a rate of 4.0% of parent reported reactions to peanut in a population study in Australia ⁹. Furthermore, these cases may be the non-preventable cases as the LEAP study reports the occurrence of peanut allergy despite early introduction in both the SPT negative and positive cohorts ⁵.

We compared this case series with a group of age-matched controls - infants seen in our allergy clinic who successfully introduced peanut early and did not develop peanut allergy (Table 2). The median age of peanut introduction was 7 months (in the case series) versus 10 months (in the control group), both within the recommended window of early introduction. Additionally,

comparison of family history, presence of eczema, other food allergy, asthma or allergic rhinitis revealed no significant differences between the two groups.

We report that in a minority of infants, peanut allergy may develop despite successful early introduction and regular consumption. Those with irregular consumption may be even more at risk, although further investigation is required, as the optimal frequency and dosing of peanut remains to be elucidated. These cases likely represent a small minority of infants who introduce peanut early.

Our results provide new information on early peanut introduction that can help healthcare providers to educate patients accordingly. It is important to be aware that early introduction is not foolproof; allergy likely develops only in a minority of infants who undergo screening and it is possible for infants with no risk factors and for whom testing is not indicated by guidelines to develop peanut allergy. Further studies are required to advise on the optimal frequency and amount of peanut consumption, which may even vary between infants depending on their baseline risk.

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Table 1: Patient Characteristics (peanut allergy case series)

Patient	1	2	3	4	5	6	7
Sex	M	F	M	M	M	F	F
Age at initial peanut introduction (months)	7	12	6	6	<15	6	7
Age at peanut reaction (months)	12	13	12	8	15	7	8
Duration of peanut consumption (months)	4	1	6	2	NA	1	1
Frequency of peanut consumption (times/week)	2-3	2-3	Irregular	1	Irregular	2-3	2-3
Amount of Peanut Exposure	1 tsp peanut butter	3 tsp peanut butter	2 tsp peanut butter	1/8 tsp peanut butter	2 tsp peanut butter	2 tsp peanut butter	2 tsp peanut butter
Age at testing (months)	12	24	12	12	17	7	7
Peanut SPT at baseline (initial introduction)	NA	0/0	NA	0/0	NA	0/0	0/0
Peanut SPT following allergic reaction (wheal/mm)	7/20	12/30	4/15	NA	13/-	1/2	NA
slgE peanut at baseline (initial introduction kU/L)	NA	NA	NA	NA	NA	<0.10	0.15
slgE peanut following allergic reaction (kU/L)	5.41	1.37	1.41	1.96	NA	<0.10	NA
IgE mediated reaction (Y/N)	Yes	Yes	Yes	Yes	Yes	No	No
FPIES reaction (Y/N)	No	No	No	No	No	Yes	Yes
Co-Existing Atopic Dermatitis	No	Yes	Yes	Yes	Yes	Yes	Yes

Co-existing asthma/wheeze	Yes	No	No	No	No	No	No
Co-existing allergic rhinitis	No	No	No	Yes	Yes	No	No
Other co-existing food allergies	Yes	Yes	No	Yes	Yes	Yes	Yes
Family History of Atopic Disease	FA, A, AR, E	A, AR	A, E	AR	None	A, AR, FA	E
Oral Graded Challenge Prior to Reaction performed (cumulative dose: 3.96g)	No	Yes	No	Yes	No	Yes	Yes

tsp: teaspoon

A: Asthma

E: Eczema

AR: allergic rhinitis

FA: Food allergy

NA: not available

Table 2: Control group patient characteristics

Age (months)	Gender	Skin test wheal (mm) peanut extract	Peanut specific IgE (kU/L)	Cumulative amount consumed during OFC	Other food allergies	Asthma/ wheeze	Allergic Rhinitis	Eczema	Family history of atopy (first degree relatives only)
8	M	3	0.1	2 g	Yes	No	No	Yes	A, AR
10	M	0	0.12	3.9g	Yes	No	No	Yes	AR, E, FA
15	M	4	NP	3.9g	None	No	No	Yes	Not documented
12	M	2	0.55	3.9g	Yes	No	No	Yes	AR, A, E
8	F	1	<0.1	4g	None	No	No	Yes	None
13	F	NP	<0.1	2g	None	No	No	Yes	None
8	M	0	NP	2g	Yes	Yes	No	Yes	A
10	M	3	<0.1	2g	Yes	No	No	Yes	A, FA
16	F	1	NP	2g	Yes	No	No	Yes	None
4	F	4	NP	2g	None	No	No	Yes	FA, E, AR

NP: not performed

A: asthma

FA: food allergy

AR: allergic rhinitis

E: eczema