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Relevance of sensitization to legumes in peanut-allergic children

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Abstract

Background: Legume consumption has increased during the two past decades. In France, legumes are responsible for 14.6% of food-related anaphylaxis in children, with peanut as the main allergen (77.5%). Few studies have demonstrated cross-reactivities between peanut and other legumes. The aim of this study was to determine prevalence and relevance of sensitization to legumes in peanut-allergic children.

Methods: All children, aged of 1–17 years, admitted to the Pediatric Allergy Department of the University Hospital of Nancy between January 1, 2017 and February 29, 2020 with a confirmed peanut allergy (PA) and a documented consumption or sensitization to at least one other legume were included. Data were retrospectively collected regarding history of consumption, skin prick tests, specific immunoglobulin E (IgE), prior allergic reactions, and oral food challenges for each legume.

Results: Among the 195 included children with PA, 122 were sensitized to at least one other legume (63.9%). Main sensitizations were for fenugreek ($N = 61$, 66.3%), lentil ($N = 38$, 42.2%), soy ($N = 61$, 39.9%), and lupine ($N = 63$, 34.2%). Among the 122 sensitized children, allergy to at least one legume was confirmed for 34 children (27.9%), including six children who had multiple legume allergies (4.9%). Lentil, lupine, and pea were the main responsible allergens. Half of allergic reactions to legumes other than peanut were severe.

Conclusion: The high prevalence of legume sensitization and the frequent severe reactions reported in children with PA highlight that tolerated legume consumption should be explored for each legume in the case of PA, and sensitization should be investigated if not.

KEYWORDS
allergy, children, cross-reactions, legumes, peanut, sensitization

1 | INTRODUCTION

Food allergens are the most common triggers of allergic reactions in childhood. In France, legumes are responsible for 14.6% of food-related anaphylaxis in children, with peanut recognized as the main allergen (77.5%).[1] Other causative legumes identified in France and Europe are as follows: soy, lentils, peas, beans, lupine, and fenugreek.[2] Most of these legumes are not mentioned in the list of 14 priority food allergens. Moreover, legume consumption is increasing worldwide due to their high protein content, low levels of unsaturated fats, low cost of production, and the desire to achieve a more vegetarian, healthy, and sustainable diet.[3–5]

Previous studies have reported the risk of cross-reactivity between peanut allergy (PA) and other legumes, but in a small number of patients, with little data regarding the relevance of sensitization.[6–10] Nevertheless, seed storage protein allergens, members of the cupin, and prolamin superfamily (e.g., 7S and 11S globulins or 2S albumin) are similar allergens to legumes.[11–13] Therefore, cross-sensitization to legumes other than peanut without a relevant allergy may exist, particularly in patients sensitized to the common cupins and prolamins mentioned above.[14–16]

The aim of this study was first to determine the prevalence of sensitization and allergy to other legumes in children with PA and second to determine the severity of these allergic reactions.

Key message

Among children allergic to peanut, at least two-thirds were sensitized to one other legume, and legume allergy was diagnosed in one-quarter of the sensitized patients. Lentil, lupine, and pea were the main responsible allergens. Fenugreek allergy was found for almost 10% of sensitized children. Half of allergic reactions to legumes other than peanut were severe reactions. The high prevalence of legume sensitization and the frequent severe reactions reported in children with peanut allergy highlight that tolerated legume consumption should be explored for each legume in the case of peanut allergy, and sensitization should be investigated if not.

2 | METHODS

2.1 | Study population

All children with confirmed PA admitted to the Pediatric Allergy Department of the Nancy University Hospital between January 1, 2017 and February 29, 2020 were included. Children younger than 1 year old, or older than 17 years at diagnosis of PA and children without any data regarding sensitization and oral tolerance to any other legumes, were not included. PA was defined as a history of relevant allergic reaction associated with sensitization to peanut, or as a positive oral food challenge (OFC) to peanut.

2.2 | Data source

Data were retrospectively collected from each patient's medical record. The clinical database was declared to the French Data Protection Authority (2019PI247).

Children who underwent an OFC and their parents were informed by the physician regarding the use of clinical data and gave their written consent.

This study was reviewed and approved by the Ethical Committee of the University Hospital of Nancy.

2.3 | Collected variables

Collected variables included social and demographic characteristics, atopic comorbidities, history of PA, and legume cosensitization or coallergy, including prior allergic reaction, OFC, skin prick test (SPT), and specific immunoglobulin E (sIgE). Allergic reaction was considered relevant if at least one of these symptoms was reported by parents after ingestion of peanut: urticaria, angioedema, rhino conjunctivitis, abdominal pain, vomiting, asthma, and systemic anaphylaxis.

Children's allergic status to each legume was evaluated by consumption, sensitization, and allergic reaction. When there was a history of tolerated consumption for one legume, sensitization was not evaluated. When sensitization was found without a history of tolerated consumption or allergic reaction, an OFC was suggested.

Regarding SPT, histamine chlorhydrate (10 mg/ml) positive control was used for the majority of children ($N = 151$, 77.4%). If not, codeine phosphate (9%) was used. SPT were performed with fresh food extracts conditioned in ground form by the hospital food laboratory according to standard operating procedures.[17] Fresh food extracts were humidified in saline solution just before prick testing.

sIgE assays were performed by ImmunoCAP fluorescence enzyme immunoassay (Thermo Fisher Scientific®) for peanut and peanut recombinants (rAra h 1, rAra h 2, rAra h 3, rAra h 6, rAra h 8, and rAra h 9), chickpea, fenugreek, lentil, lupine seed, pea, soy, and soy recombinants (rGly m 4, rGly m 5, and rGly m 6). There was no sIgE available for bean or broad bean.

Sensitization was defined as a positive SPT (wheal size ≥3 mm) or a positive sIgE (≥0.35 kU/L). OFCs were described with symptoms and severity of allergic reaction according to Astier's classification[18] and cumulative reactogenic dose. Regarding severity, data from prior allergic reaction were used when no OFC data were available. Some legumes could be consumed in different forms

(raw lupine flour, grilled lupine flour, pea protein, green pea, soy protein, soy dessert, soy drink, and soybean flour). When there were two OFCs for the same legume but in a different consumption form, the OFC with the most severe reaction was retained. Oral allergy syndrome (OAS) was not considered as an allergic reaction when isolated.

The protein content of peanut (26.1%), flageolet bean (5.6%), white bean (9.63%), broad bean (5.6%), fenugreek (27.1%), green lentil (10.1%), lupine (36.3%), green pea (6.4%), soy dessert (4.1%), soy drink (3.63%), and soy flour (39.2%) was taken from the Ciqual table.[19] OFCs were considered negative for each legume if the cumulative dose was superior or equal to 2 grams of protein, except for fenugreek. Indeed, for fenugreek, 2 grams of protein is far from the amount served in real life. Consequently, an OFC was considered negative for a cumulative dose of at least 0.27 g of protein (which represents 10 g of curry powder with 10% fenugreek).

2.4 | Statistical analysis

Characteristics of the sample were described using percentages for categorical variables and median, first and third quartiles values for continuous variables. Regarding diagnostic values, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for different predetermined cutoffs: 3, 5, and 8 mm for SPT, and 0.35, 3.5, and 15 kU/L for sIgE. These statistical analyses were performed using SAS 9.4 software (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics and peanut allergy

Among the 195 peanut-allergic children included, 69.7% were boys, 62.4% had another food allergy (in addition to legumes), and 98.4% had at least one other atopic disease. Among the 118 children having another food allergy, the main food allergens were egg (*N* = 68, 57.6%), cow's milk (*N* = 39, 33.0%), cashew nut (*N* = 46, 39.0%), pistachio (*N* = 28, 23.7%), and hazelnut (*N* = 36, 30.5%).

The median age at diagnosis of PA was 4 years old [2.0–6.0]. Anaphylactic reactions (i.e., Astier's score ≥3) were found in 51.5% of inaugural reaction and 69.2% OFC reactions. There was no grade five. All children were sensitized to at least one peanut storage protein apart from one child for whom rAra h 6 IgE assay was not available.

The characteristics of the study population are shown in Table 1.

TABLE 1 Characteristics of study population and peanut allergy (*N* = 195)

	N	%	Med[a] (Q1-Q3)[a,b]
Gender (male)	136	69.7	
Atopic comorbidities			
Another food allergy (in addition to legumes)[c]	118	62.4	
Allergy or sensitization to inhalant allergens	149	76.4	
Other atopic diseases[c]	189	98.4	
Atopic dermatitis[c]	161	84.7	
Asthma[c]	130	68.1	
Rhino-conjunctivitis[c]	81	42.4	
Age at diagnosis of PA (years)	195		4.0 (2.0–6.0)
Discovery mode of PA			
OFC for sensitization	65	33.3	
Prior allergic reaction	130	66.7	
SPT for native peanut (mm)[c]	193		10.0 (7.5–14.0)
Specific IgE (kU/L)[c]	194		
Peanut	168		35.9 (8.1–165.5)
r Ara h 1	189		3.6 (0.3–30.8)
r Ara h 2	194		18.2 (3.9–76.3)
r Ara h 3	189		0.5 (0.0–9.0)
r Ara h 6	86		14.1 (3.5–51.4)
r Ara h 8	168		0.0 (0.0–6.8)
r Ara h 9	170		0.0 (0.0–0.1)
Prior allergic reaction to peanut	130	66.7	
Severity of prior allergic reaction to peanut (Astier's score)			
1	29	22.3	
2	34	26.2	
3	31	23.8	
4	36	27.7	
Oral Food Challenge to peanut	150	76.9	
Severity of Oral Food Challenge reaction to peanut (Astier's score)[c]			
1	9	6.0	
2	37	24.8	
3	47	31.5	
4	56	37.7	
Cumulative reactogenic dose for peanut (mg of protein)[c]	149		56.1 (19.3–204.9)
Eliciting dose for peanut (mg of protein)	150		39.1 (13.0–104.4)

[a]med: median; Q1: first quartile; Q3: third quartile.

[b]Values were non-normal distributed.

[c]Missing values: another food allergy: 6; other atopic diseases: 3; atopic dermatitis: 2; asthma: 1; rhino-conjunctivitis: 1; SPT for native peanut: 2; specific IgE: 1; severity of oral food challenge reaction (Astier's score): 1; cumulative reactogenic dose for peanut: 1.

3.2 | Prevalence of legume sensitization

Regarding the evaluation of prior consumption, sensitization, and allergy to legumes, lupine was the most frequently evaluated legume, followed by soy, pea, lentil, fenugreek, chickpea, bean, and broad bean (Table 2). For most patients, sensitization was not systematically evaluated for each legume because of a history of tolerated consumption. There were no data concerning sensitization status for four children,

TABLE 2 Evaluation of allergy status

	Exploration	Prior consumption				Sensitization (SPT and/or IgE)[a]	Positive OFC[b]
		Prior allergic reaction	Tolerated consumption	No history of consumption	Not reported		
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Lupine	185 (94.9)	4 (2.2)	8 (4.3)	81 (43.8)	92 (49.7)	63/184 (34.2)	10/18 (55.6)
Pea	172 (88.2)	7 (4.1)[c]	112 (65.1)	7 (4.1)	46 (26.7)	52/137 (38.0)	1/22 (4.5)
Soy	161 (82.6)	4 (2.5)	47 (29.2)	38 (23.6)	72 (44.7)	61/153 (39.9)	2/25 (8.0)
Lentil	148 (75.9)	8 (5.4)	104 (70.3)	9 (6.1)	27 (18.2)	38/90 (42.2)	0/2 (0.0)
Fenugreek	103 (52.8)	4 (3.9)	37 (35.9)	33 (32.0)	29 (28.2)	61/92 (66.3)	4/25 (16.0)
Chickpea	100 (51.3)	2 (2.0)	36 (36.0)	15 (15.0)	47 (47.0)	27/81 (33.3)	0/2 (0.0)
Bean	89 (45.6)	0 (0.0)	49 (55.1)	6 (6.7)	34 (38.2)	14/65 (21.5)	0/2 (0.0)
Broad bean	74 (37.9)	0 (0.0)	19 (25.7)	16 (21.6)	39 (52.7)	19/62 (30.6)	0/1 (0.0)

[a]Sensitization was considered positive if sIgE was ≥ 0.35 kU/L and/or SPT was ≥ 3 mm.

[b]Positive OFC to raw lupine flour: 3, grilled lupine flour: 3, raw and grilled lupine flour: 4; soy protein:1, soy flour: 1; green pea and pea protein: 1.

[c]History of prior allergic reaction to green pea for seven patients, in addition to split pea for two patients. There was no prior allergic reaction to pea protein.

who were only evaluated using prior consumption for each legume. Only 29 children had a history of exploration for each legume.

Among the 191 children with data regarding sensitization to legumes, 63.9% (*N* = 122) were sensitized to at least one legume (Table 2). Main sensitizations were to fenugreek, followed by lentil, soy, pea, lupine, chickpea, broad bean, and bean.

Characteristics of sensitization for each legume are shown in Table 3.

3.3 | Prevalence and severity of legume allergy

Allergy to at least one legume was confirmed in 34 children (17.4% of the population study and 27.9% of the sensitized children). Among them, six children (3.1%) had multiple allergies to legumes (pea and lentil; pea and soy; fenugreek and soy; fenugreek and lupine; pea, lentil, and lupine; chickpea and lentil; chickpea and pea).

Among sensitized children, eight of 38 were allergic to lentil (21.0%), 12/63 were allergic to lupine (19.0%), eight of 52 were allergic to pea (15.4%), six of 61 were allergic to fenugreek (9.8%), five of 61 were allergic to soy (8.2%), and two of 27 were allergic to chickpea (7.4%). The prevalence of legume allergy and sensitization is detailed in Figure 1.

Regarding the severity of allergy (prior allergic reaction and OFC combined), most patients had a history of anaphylactic reaction, including 100% for soy, 50.0% for lupine, 62.5% for lentil, 50.0% for chickpea, and 50.0% for pea, except fenugreek (33.3%) (Figure 2). Mild isolated cutaneous reactions were rare. Mean values of cumulative reactogenic dose for each legume are detailed in Table 4.

3.4 | Diagnostic value of skin prick tests and specific IgE

Diagnostic values were evaluated for each legume and are detailed in Table S1.

Regarding fenugreek, sIgE <3.5 kU/L and SPT <5 mm both had NPVs of 100%. The highest PPV was found for sIgE values≥15 kU/L (50.0%). PPVs regarding SPT were lower than 25%.

Regarding lupine, NPVs for SPT <3 mm and sIgE <0.35kU/L were 100%. The highest PPV was 76.9% for raw lupine flour, SPT ≥ 5 mm, and 100% for sIgE ≥ 15 kU/L.

Diagnostic values concerning pea and lentil were low. There were insufficient data to analyze diagnostic values of sIgE and SPT for allergies to chickpea, bean, and broad bean.

4 | DISCUSSION

Among our cohort of 195 peanut-allergic children, sensitization to at least one other legume was frequent, and one in five sensitized children were allergic to at least one other legume. The main sensitizations were found for fenugreek, lentil, soy, and lupine. Among sensitized children, lentil, lupine, and pea were the main culprit allergens. Anaphylactic reactions were frequent, especially for soy and lentil.

To the best of our knowledge, this is the first study evaluating clinically relevant cross-reactivity concerning all legumes, especially fenugreek, in a large cohort of 195 children with PA. However, the main limitation of our study is the disparate exploration of consumption and sensitization for each legume, with variations from 37.9% for broad bean to 94.9% for lupine. This is mostly due to the retrospective data collection, with changes in practice and awareness over time. This might have affected estimation of the prevalence of sensitization and allergy for each legume. Furthermore, when regular tolerated consumption was reported, we were not able to evaluate the precise amount of protein and did not perform an OFC. Another limitation is open OFC with a cumulative reactogenic dose of 2 g of protein, which is lower than in the PRACTALL recommendation but close to serving size.

Although relevant cross-reactivity between tree nuts and peanut has been well demonstrated,[20,21] cross-reactivity between

TABLE 3 Prevalence and description of legume sensitization in peanut-allergic children

	Total, *N*	Positive test[a], *N* (%)	med[b] (Q1-Q3[b]) [c]
Bean			
Skin prick tests (mm)	65	14 (21.5)	
Flageolet bean	56	9 (16.1)	0.0 (0.0–1.8)
Cranberry bean	47	7 (14.9)	0.0 (0.0–2.0)
Kidney bean	46	6 (13.0)	0.0 (0.0–2.0)
Broadbean			
Skin prick test (mm)	62	19 (30.6)	0.0 (0.0–3.5)
Chickpea			
Skin prick test (mm)	81	25 (30.9)	1.0 (0.0–4.0)
Specific IgE (kU/L)	4	4 (100)	1.5 (0.8–2.7)
Fenugreek			
Skin prick test (mm)	91	57 (62.6)	4.0 (1.0–8.0)
Specific IgE (kU/L)	34	32 (94.1)	10.2 (2.1–20.0)
Lentil			
Skin prick test green lentil (mm)	90	37 (41.1)	1.0 (0.0–5.5)
Specific IgE (kU/L)	12	12 (100)	5.8 (1.8–14.1)
Lupine			
Skin prick tests (mm)	183	54 (29.5)	
Raw lupine flour	144	48 (33.3)	1.0 (0.0–3.8)
Lupin seed	140	21 (15.0)	0.0 (0.0–2.0)
Specific IgE (kU/L)	43	39 (90.7)	2.7 (1.2–6.3)
Pea			
Skin prick tests (mm)	137	52 (38.0)	
Pea protein	103	37 (35.9)	1.5 (0.0–4.5)
Golden pea	64	29 (45.3)	2.0 (0.0–5.5)
Green pea	78	32 (41.0)	2.0 (0.0–4.0)
Specific IgE (kU/L)	15	14 (93.3)	6.3 (1.7–9.8)
Soy			
Skin prick tests (mm)	153	51 (33.3)	
Soy flour	113	40 (35.4)	1.5 (0.0–3.5)
Soy protein	106	25 (23.6)	1.0 (0.0–2.5)
Soy drink	24	13 (54.2)	3.0 (1.3–6.3)
Soy dessert	23	6 (26.1)	1.0 (0.0–3.0)
Specific IgE (kU/L)	45	36 (80.0)	
Soy	43	35 (81.4)	3.1 (0.6–9.0)
r Gly m 4	27	13 (48.1)	0.1 (0.0–4.0)
r Gly m 5	20	15 (75.0)	2.7 (1.0–7.4)
r Gly m 6	19	17 (89.5)	4.4 (0.6–12.8)

[a]Skin prick test was considered positive if ≥ 3 mm; specific IgE was considered positive ≥ 0.35 kU/L.

[b]med: median; Q1: first quartile; Q3: third quartile.

[c]Values were non-normal distributed.

legumes has largely been demonstrated in a few in-vitro studies without clinical relevance for most legumes.[10,13,15,16]

Little is known about the prevalence of cross-allergy between peanut and other legumes. A recent study evaluated, for the first time, the prevalence of allergy to other legumes and found it to be present in 7.9% of a large cohort of 317 peanut-allergic children. Among them, 66.6% were sensitized to at least one other legume.[21] As in our study, there was no allergy observed to bean or broad bean, and fenugreek was not explored. We found similar data regarding soy, pea, and chickpea but found a higher prevalence of lupine allergy in our cohort (3.0% vs. 19.0% in our study) with similar sensitization rates (31.9% vs. 34.2%). Lupine is one of the most studied legumes after peanut, but the prevalence of cross-allergy to peanut varies from 3% to 30% according to different studies.[6,7,21,22] Half of lupine-allergic children in our study had a history of severe reactions to lupine, sometimes with very low doses during an OFC.

Regarding pea, lentil, and chickpea, cross-reactivities among them, independent of PA, are most often observed in the Mediterranean area, due to high consumption.[23] In our study, lentil and pea were responsible for 44.1% of cross-allergic reactions with peanut ($N = 15$). Allergy to chickpea was found for two patients, associated with an allergy to pea for one patient and to lentil for the other patient.

While only six pediatric cases of fenugreek allergy have been reported in the literature,[9,24–26] almost 10% of sensitized children in our study had a fenugreek allergy. In our study, allergy to fenugreek was diagnosed by a positive OFC for sensitization without prior consumption in 50% of cases. Only one-third of patients had a severe reaction, but all with low cumulative reactogenic dose (maximum 271 mg of protein), which may underestimate the risk in real life. It was the most interesting legume regarding diagnostic values, with 100% NPV with an SPT value inferior to 5 mm and 93% NPV with an sIgE value inferior to 15 kU/L. Fenugreek may be a real threat regarding accidental anaphylaxis, as it is not included in the list of priority allergens and mostly consumed in hidden forms (in mixed spices, Indian or exotic dishes, some cheese, and some medication). Fenugreek consumption or sensitization should be systematically explored in children with PA.

Soybean is considered one of the major food allergens worldwide. In the literature, two types of allergy to soy are described: an early-onset allergy by prior sensitization to storage proteins rGly m 5 and rGly m 6 and a late-onset, less severe allergy by prior sensitization to rGly m 4, birch pollen (rBet v 1), and/or peanut (rAra h 8).[27,28] Some studies seem to indicate that, if most soy-allergic children were also allergic to peanut, the reverse could not be systematically evidenced. For example, Patel et al.[8] found that only 3.0% of children with PA had an allergy to soy. This corresponds with our findings, where only 8.2% children with PA were allergic to soy. However, in children with PA, reactions seem to be more severe,[29,30] which is also in agreement with our study (all had a history of severe reactions). Complete sIgE explorations were achieved for only three patients with soy allergy (60%), and all had positive sIgE for rGly m 5 and rGly m 6, with a lower sensitization to rGly m 4 (<1 kU/L).

Regarding severity of allergy, 50% of the reactions to legumes were severe, frequently with manifestations of asthma. Most of the study population had atopic comorbidities, including asthma, that may have contributed to the severity of allergic reactions.

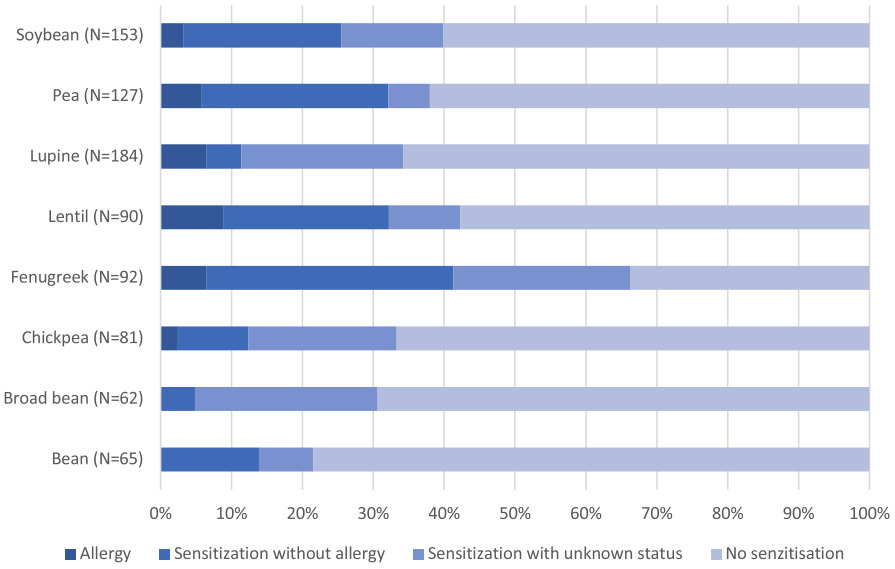

FIGURE 1 Legume allergy and sensitization rates, with frequency expressed in percentage of children

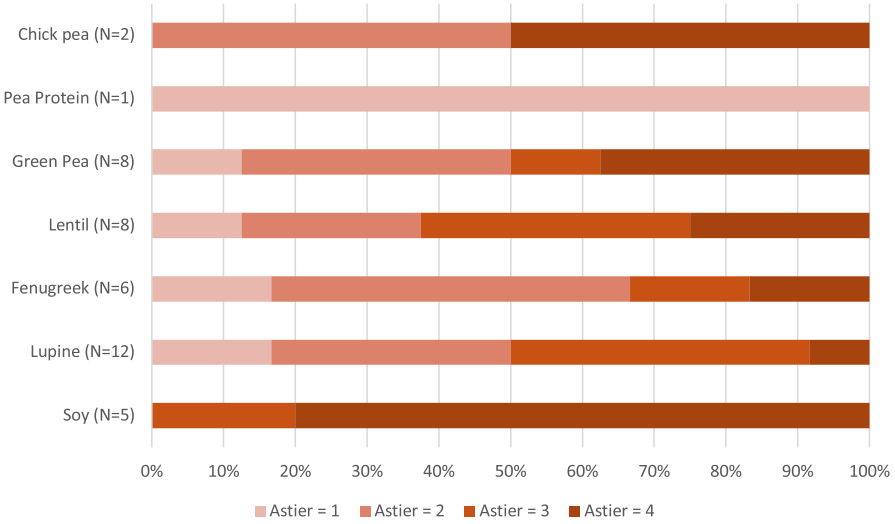

FIGURE 2 Severity of legume allergy according to Astier's score, expressed in percentage of children

TABLE 4 Mean values of cumulative reactogenic doses for each legume during oral food challenge

	Total, *N*	Mean value (mg of protein)	Min – max (mg of protein)
Fenugreek	4	118.2	7.9–271.0
Lupine			
Raw lupine flour	7	1123.8	23.6–3811.5
Grilled lupine flour	7	1697.3	83.5–3194.4
Pea			
Green pea	1	448	
Pea protein	1	2000	
Soy			
Soy flour	1	5880	
Soy protein	1	7000	

5 | CONCLUSION

The high prevalence of legume sensitization reported in our study highlights the need to explore legume consumption in children with PA, and the need to investigate sensitization in the absence of consumption. Furthermore, in case of allergy to another legume than peanut, anaphylactic reactions were frequent. This result testifies to the potential severity of these allergic reactions which can be avoided by a targeted allergy assessment. Further research with a prospective and systematic exploration of all legumes is needed to have a better evaluation of the prevalence of allergy to legumes, and the risk of peanut-allergic children. Furthermore, comprehensive reporting of anaphylaxis to legumes to the anaphylaxis registry is urgently needed to discuss the expansion of priority allergens to some legumes. As only three legumes (peanut, soy, and lupine) are included in the list of the 14 priority food allergens, the

expansion of the list with legumes frequently consumed in a hidden form, such as pea protein and fenugreek would allow to avoid food anaphylaxis induced by hidden forms and improve children's quality of life.

AUTHOR CONTRIBUTIONS

Timé Muller: Conceptualization (equal); data curation (lead); writing – original draft (lead). **Amandine Luc:** Formal analysis (lead); methodology (equal). **Tania Adam:** Resources (supporting); writing – review and editing (supporting). **Sophie Jarlot-Chevaux:** Resources (equal); writing – review and editing (supporting). **Pascale Dumond:** Resources (equal); writing – review and editing (supporting). **Cyril Schweitzer:** Writing – review and editing (equal). **Françoise Morel-Codreanu:** Writing – review and editing (equal). **Amandine Divaret-Chauveau:** Conceptualization (lead); data curation (supporting); methodology (equal); resources (lead); supervision (lead); writing – review and editing (lead).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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