ORIGINAL ARTICLE

Flaxseed allergy: insights from a case series

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Summary

Background. Flaxseed allergy is a rare and potentially underdiagnosed condition. In recent years, sensitization to flaxseed has increased due to its growing presence in the human diet. This study presents three distinct cases of flaxseed allergy and discusses the strengths and limitations of current diagnostic tools in identifying this emerging allergy. **Methods.** Each case underwent a detailed

clinical history followed by an allergological evaluation using *in vivo* testing (skin prick-to-prick) and in vitro methods (serum specific IgE testing with singleplex and multiplex immunoassays) for flaxseed and other suspected seeds or tree nuts. **Results.** Case 1: A male patient, previously diagnosed with pumpkin seed allergy, experienced multiple episodes of urticaria and angioedema following ingestion of bread containing unspecified dark seeds. Testing revealed sensitization to flaxseed, pumpkin, sunflower, sesame seeds and storage proteins from soy, walnut, and hazelnut. Case 2: A male patient developed cutaneous symptoms after ingesting an energy bar. Testing showed positivity only to flaxseed, while results for other seeds and tree nuts were negative. Case 3: A female patient with repeated episodes of labial angioedema and anaphylaxis, initially misdiagnosed with sesame allergy, was found to be allergic to flaxseed. **Conclusions.** Flaxseed allergy remains a rare but emerging condition that is difficult to diagnose, partly due to its frequent omission from ingredient labels and the absence of specific allergenic molecules in commercial diagnostic tests. Future regulatory consideration should evaluate the inclusion of flaxseed among priority food allergens.

Key words

Flaxseed allergy; anaphylaxis; molecular allergy; hidden allergens; food allergy.

IMPACT STATEMENT

We described three distinct cases of flaxseed allergy and highlighted the strengths and limitations of current diagnostic tools in identifying this emerging allergy.

Introduction

Flaxseed is the seed of *Linum usitatissimum*, an annual plant of Central Asian and Arabian origin, historically used in the textile industry for its fibers. The oil extracted from flaxseed has applications in manufacturing (e.g., paints, inks) and in health products (e.g., laxatives, healing creams). Flaxseed is also included in animal feeds (birds, cats, dogs, horses, etc.) (1,2). Recently, flaxseed has been incorporated into the human diet as a "superfood" due to its high content of dietary fiber and polyunsaturated fatty acids with anti-inflammatory, cardiovascular, and antioxidant properties (3). Flaxseed allergy was first reported by Black in 1930 (4). Since then, additional reports have described anaphylaxis, occupational asthma (5), and contact dermatitis (6). Case of anaphylaxis after ingestion of grains, coffee, biscuits, yoghurts, milkshake, and salad containing flaxseed (7-11) were described. Recently flaxseed allergy it was also described in infants through cutaneous sensitization (12,13). Because flaxseed can be a hidden allergen, diagnosis is often delayed or missed. This study presents three illustrative cases of flaxseed allergy, with different clinical and laboratory findings.

Materials and Methods

Allergological investigations of all the cases included skin prick-to-prick tests with flaxseed and other potentially relevant seeds using whole and toasted seeds, specific IgE measurements for flaxseed and other seed extracts with singleplex assay (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden), and with a multiplex assays (ALEX^2, Macro Array Diagnostics, Vienna, Austria). The multiplex platform includes 300 allergen preparations (117 extracts and 178 molecular components) coupled to nanoparticles. Both ImmunoCAP and multiplex assays were performed following the manufacturers' instructions and results were reported in kUA/L. The positivity threshold were fixed at 0.1 kUA/L and 0.30 kUA/L, respectively.

Results

Clinical cases

Case 1:

In 2015, a 34-year-old man was referred to our Allergy Unit due to the occurrence of urticaria, angioedema, and dysphagia a few minutes after ingestion of yoghurt containing pumpkin seeds. Suspecting pumpkin seed allergy, a skin prick-to-prick test with toasted pumpkin seeds was performed and resulted positive (18 mm wheal). Sensitization to pumpkin seeds was further confirmed by serum specific IgE measurement for pumpkin seed extract (22.80 kU/L), supporting a diagnosis of pumpkin seed allergy, even though it was not possible to perform the oral challenge test because the patient refused to undergo it.

Concomitantly, specific IgE testing revealed sensitization to sesame (3.20 kU/L), soybean (0.58 kU/L), hazelnut storage protein Cor a 9 (4.94 kU/L), and soybean storage protein Gly m 6 (0.72 kU/L). However, the patient reported tolerance to sesame seeds, soybeans, tree nuts, and legumes, and was therefore advised to avoid only pumpkin seeds.

In 2024, the patient returned to our Allergy Unit with recurrence of the same symptoms within minutes after ingestion of bread containing unidentified dark seeds (excluding pumpkin, which he carefully avoided). A second allergological workup was performed, including skin prick-to-prick testing with several “dark-colored seeds” such as flaxseed, sunflower seed, and poppy seed. A positive reaction was observed only for flaxseed (12 mm wheal). Specific IgE testing confirmed sensitization to flaxseed (3.13 kU/L) with a low-level positivity to sunflower seed (0.62 kU/L). Results were negative for wheat proteins and non-specific lipid transfer proteins (nsLTPs).

A multiplex assay (ALEX2) confirmed the previous sensitization to pumpkin seed (21.69 kU/L), with low-level sensitization to poppy seed (0.55 kU/L) and to walnut storage proteins Jug r 4 (2.57

kU/L), Jug r 6 (0.79 kU/L), as well as hazelnut storage protein Cor a 9 (1.11 kU/L). Flaxseed extract and molecular components were unavailable in this assay.

Since the initial diagnosis of pumpkin seed allergy, the patient reported tolerance to other seeds (except pumpkin), although he could not recall which ones specifically. The involvement of pumpkin seeds in the most recent reaction was excluded, as the bakery later confirmed the exclusive use of flaxseed in the bread. While a primary sensitization to pumpkin seed is likely, co-sensitization or cross-reactivity with flaxseed and other seeds cannot be ruled out.

The patient was advised to avoid pumpkin, flaxseed, and also other seeds (i.e., sunflower, poppy, and sesame) as a precaution. An epinephrine auto-injector was prescribed and he was encouraged to continue consuming tree nuts that he still tolerated.

Case 2:

A 54-year-old man with no prior allergy history developed cutaneous symptoms after about 2 hours from eating an energy bar containing various nuts and seeds (i.e. peanuts, almonds, hazelnuts, cashews, flaxseeds, sunflower seeds, and pumpkin seeds). He tolerated most ingredients later (e.g. peanuts, walnuts, hazelnuts, sunflower seeds, and pine nuts), but avoided cashews and pistachios by personal choice. Specific IgE was positive only for flaxseed (0.74 kU/L), and negative for peanuts, pistachios, cashews, almonds, pumpkin seeds, sunflower seeds, and lupine seeds. Multiplex testing revealed a sensitization to PR-10 proteins: Bet v 1 (1.18 kU/L), Cor a 1 (7.31 kU/L), Fag s 1 (2.48 kU/L), but not to nuts or seeds. Skin prick-to-prick only with heated whole flaxseed was carried out (to exclude any possible interference with the contextual sensitization to PR-10) and it resulted positive (12 mm wheal), confirming a genuine clinically relevant sensitization. A diagnosis of flaxseed allergy was made, and the patient was advised to avoid flaxseed and epinephrine auto-injector was prescribed. After about a year from our indications, the patients was contacted again

and he reported to tolerate also almond, cashew, and pumpkin seeds without reactions but he continued to avoid flaxseeds. This last information further supports a flaxseed allergy.

Case 3:

A 39-year-old woman, initially presumed to have sesame allergy by her general practitioner, since reported episodes of labial angioedema after about an hour from consuming sesame-containing bread, but without having undergone allergy tests. Avoidance of sesame did not resolve symptoms, and she later experienced two episodes of anaphylaxis (after eating flatbread and pizza). A history of rhinitis upon exposure to bird feed was reported. Skin prick-to-prick testing was negative for sesame (both seeds and sesame paste "tahini"), and for all other seeds tested (i.e. poppy, sunflower, pumpkin, quinoa and Chia seeds) except heated flaxseed (15 mm wheal). Specific IgE was strongly positive for flaxseed (58.1 kU/L) and negative for sesame, millet, lupine, and soy. Multiplex testing excluded a sensitization to wheat proteins (i.e. wheat, gliadin, gluten, Tri a 19, Tri a 14) and other seeds (i.e. poppy, sunflower, quinoa, and sesame seeds) but only revealed a sensitization to walnut storage proteins 7/8S globulins (Jug r 6). However this last sensitization had no clinical relevance because the patient reported to tolerate walnuts without problems. The flatbread and pizza involved were later confirmed to contain linseed flour and moreover it was also found that bird feed contained flaxseeds. Diagnosis of flaxseed allergy was established, and avoidance with epinephrine prescription was recommended.

In Table 1 are resumed the three cases of flaxseed allergy.

Discussion and conclusions

Flaxseed allergy is considered rare and may be underdiagnosed due to its omission from mandatory allergen labelling regulations. Although sensitization rates range from 0.54% to 1.08%, the estimated prevalence of clinically confirmed allergy is considerably lower, approximately 0.01–0.02% (14). Flaxseed is composed of significant proportions of oil (30–46%), protein (18–30%),

fiber (20–35%), ash (3–4%), and water (4–8%) (15). Its oil is particularly rich in essential polyunsaturated fatty acids, including n-3 alpha-linolenic acid and n-6 linoleic acid.

Proteomic analysis of flaxseed has identified four principal protein classes: a) Seed storage proteins, including 11S/7S globulins and 2S albumins; b) Oleosins**;** c) Defense/stress-related proteins, such as chitinases;d) Glycolytic enzymes, including glyceraldehyde-3-phosphate dehydrogenase, fructose-bisphosphate aldolase, and malate dehydrogenase. Among seed storage proteins, 11S globulins are predominant, accounting for 41–44% of total protein content. Chitinases represent 6–10% of defense/stress-related proteins, whereas oleosins comprise approximately 2.1–2.8% (15–17).

Several flaxseed proteins have been identified as allergens, including malate dehydrogenase (8), nsLTP (9), oleosin (10), and seed storage proteins: Lin u 1 (a 2S albumin) and 11S globulins (11,18) (Table 2).

This clinical series presents various sensitization patterns:

- Case 1: Evidence of cross-reactivity with pumpkin seeds and other seed storage proteins.
- Case 2: Primary sensitization to flaxseed, supported by positive skin testing with thermally processed flaxseed and absence of co-sensitizations.
- Case 3: Initial misdiagnosis as sesame allergy; further investigation revealed flaxseed as a hidden allergen.

In each case, molecular diagnostics using the ALEX2 multiplex immunoassay were performed. Sensitization to storage proteins (11S and 7/8S globulins) was observed in Cases 1 and 3. Notably, these storage proteins, along with 2S albumins, are present in higher concentrations than other protein classes (e.g., chitinases, oleosins) in flaxseed and flax-derived products such as fine flour and protein concentrates (15,17), which may increase the likelihood of sensitization. Moreover,

storage proteins, particularly 2S albumins and 11S globulins, have been implicated in severe systemic allergic reactions in flaxseed-allergic individuals (18).

Consistent with these findings, both cases with confirmed sensitization to storage proteins (Cases 1 and 3) had histories of systemic cutaneous reactions and multiple episodes of anaphylaxis, respectively. However, the extent and clinical significance of cross-reactivity between flaxseed and homologous proteins in other allergenic seeds or nuts remains a subject of ongoing investigation. In vitro studies suggest a high degree of cross-reactivity among storage proteins, though these do not always translate into clinical symptoms. According with this last point, in Case 1 a clinical cross-reaction among flaxseed, pumpkin seeds and probably also with other seeds (i.e. sunflower and poppy seeds) it was shown; on the other hand, the sensitization to seed storage legumin-like proteins (11S globulins) of tree nuts (i.e. Jug r 4 and Cor a 9) and of legumes (i.e. Gly m 6) lacked clinical relevance due to a subsequent documented tolerance of these specific foods. Similarly, in Case 3, sensitization to walnut vicilin-like proteins (7/8S globulins) does not appear to have clinical relevance, but it may be indicative of cross-reactivity related to a primary sensitization to flaxseed vicilin. A recent study demonstrated cross-reactivity between flaxseed 2S albumins and those of cashew and peanut, as well as between flaxseed 11S globulins and those found in mustard, peanut, cashew, and pine nut (18). Additional potential cross-reactions with lupine, rapeseed, soybean, wheat, and rape pollen may involve cross-reactive carbohydrate determinants (CCDs) (14). Among edible seeds, sesame has been most extensively studied and is one of only two seeds (alongside mustard) included in the European Union's mandatory allergen labelling list. Flaxseed, currently exempt from such regulations, may evade clinical recognition.

A detailed clinical history, including possible flaxseed ingestion or respiratory exposure (e.g., via animal feed), is essential to raise diagnostic suspicion. Diagnostic workup should involve both *in vivo* (e.g., skin prick-to-prick testing using heated or extruded flaxseed and other edible seeds) and *in vitro* testing (e.g., serum-specific IgE measurement). Although current multiplex immunoassays

do not include flaxseed extracts or defined components such as Lin u 1, they can aid in excluding sensitization to other seeds or identifying co-sensitization to homologous, cross-reactive protein families (e.g., storage proteins, nsLTPs, oleosins), which can support the diagnosis and risk stratification. Nevertheless, the oral food challenge remains the diagnostic gold standard, particularly to confirm flaxseed allergy and to rule out clinically insignificant cross-reactivity. In conclusion, flaxseed allergy is a rare but emerging clinical entity associated with the increasing consumption of plant-based diets. This case series highlights:

a) The diagnostic challenge due to the lack of labeling and molecular diagnostic tools, and the need to rely on skin prick-to-prick test with seeds and, when feasible, oral food challenge to detect sensitization to potential allergens currently not available in diagnostics.

b) The potential for cross-reactivity with homologous proteins in other allergenic sources,

c) The importance of suspecting flaxseed in unexplained allergic reactions following ingestion of potentially containing foods. Current diagnostics rely on extract-based *in vivo* and *in vitro* tests; no commercial molecular diagnostics for flaxseed allergens are available. Until further evidence clarifies cross-reactivity patterns, patients should be advised about potential reactions to related seeds/nuts and provided with an emergency plan including epinephrine. Regulatory consideration should be given to the inclusion of flaxseed in the priority allergen list (19).

Contributions

Conceptualization, G.P. and D.V.; Investigation, G.P. and D.V; Writing-Original Draft Preparation, G.P.; Writing – Review & Editing, D.V.

Fundings

None

Conflict of interests

The authors declare that they have no conflict of interests.

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Cases	Allergens	Symptoms	"*In vivo*" tests	"*In vitro*" tests	
			Skin prick-to prick (diameter wheal)	**Specific IgE- singleplex**	**Specific IgE multiplex (ALEX²)**
Case 1	Yoghurt with pumpkin seeds Unidentified dark seeds	Urticaria, angioedema, and dysphagia	Heated pumpkin seed: 18 mm Heated flaxseed: 12 mm Heated sunflower seed: negative Heated poppy seed: negative	Pumpkin seed: 22.80 kU/L Flaxseed: 3.13 kU/L Sunflower seed: 0.62 kU/L Sesame seeds: 3.20 kU/L Gly m 6 (11S globulin): 0.72 kU/L Cor a 9 (11S globulin): 4.94 kU/L	Pumpkin seed: 21.69 kU/L Poppy seed: 0.55 kU/L Jug r 4 (11S globulin): 2.57 kU/L Jug r 6 (7/8S globulin): 0.79 kU/L Cor a 9 (11S globulin): 1.11 kU/L
Case 2	Energy bar containing various nuts and seeds	Itching erythematous rash	Heated flaxseed: 12 mm	Flaxseed: 0.74 kU/L Bet v 1 (PR-10): 3.51 kU/L	Bet v 1: 1.18 kU/L Cor a 1: 7.31 kU/L Fag s 1: 2.48 kU/L
Case 3	Bread, flatbread and pizza	Labial angioedema and anaphylaxis	Heated flaxseed: 15 mm	Flaxseed: 58.1 kU/L	Jug r 6 (7/8S globulin): 1.79 kU/L

Table 1: Case series summaries

Flaxseed allergens	**References**
Malate dehydrogenase	Leon F. et al (2003) [8]
Non-specific lipid transfer proteins (nsLTP)	Antolin-Amerigo D. et al (2016) [9]
Oleosin	Lleonart R. et al (2015) [10]
Seed storage proteins: 2S albumin (Lin u 1) 11S globulin	 Basagaña M. et al (2018) [11] Bueno-Díaz C. et al (2022) [18]

Table 2: Flaxseed allergens described in literature. Lin u 1 is the only allergen currently registered in the World Health Organization/International Union of Immunological Societies (WHO/IUIS) allergen database.