

Clinical Communications

Where there's smoke, there's fire: cannabis allergy through passive exposure

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Clinical Implications

- The effects of indirect exposure to cannabis (respiratory/cutaneous) on allergic sensitization are unknown. We report on 2 cases in whom cannabis sensitization and allergy with subsequent cross-reactive food allergies seem to result from exposure to cannabis smoke and/or indirect cutaneous transmission.

TO THE EDITOR:

Sensitization to cannabis mainly occurs through active consumption with exposure by inhalation, cutaneous contact, ingestion, and intravenous use. Most patients present with rhinoconjunctivitis and asthma and/or pruritus, and contact urticaria and/or angioedema. Hitherto, it has repeatedly been demonstrated that the nonspecific lipid transfer protein (ns-LTP) *Cannabis sativa* (Can s) 3 might be an important allergen.¹ Other allergenic components were described.^{2,3} However, they were not further explored in this study. Because of the high cross-reactivity between ns-LTPs, patients sensitized to ns-LTPs frequently display multiple allergies designated as the “ns-LTP syndrome.”⁴ We do not have a clear understanding of the effects of passive exposure to cannabis smoke as a potential route of allergic sensitization. Recently, we observed a 5-year-old boy who suffered from cannabis-related allergies in whom sensitization probably occurred via passive exposure to airborne cannabis allergen.⁴ Here, we report 2 additional cases in whom cannabis sensitization and allergy seem to result from passive exposure to cannabis smoke and/or indirect cutaneous transmission.

A thorough history was taken and complemented by a standardized questionnaire on allergic symptoms. Informed consent was obtained for all patients in accordance with the Declaration of Helsinki. Skin prick tests (SPT) were performed with an ns-LTP-rich extract from Can s prepared as described elsewhere.⁴ Cutaneous reactions were read after 15 minutes and a wheal exceeding 3 mm was considered positive. Total IgE and specific IgE (sIgE) to industrial hemp, rCan s 3 (*C. sativa*), rPru p 3 (*Prunus persica*), and bromelain (biomarker for sensitization to cross-reactive carbohydrate determinants [CCD]) were measured. Specific IgE was also quantified to the CCD-free recombinant (r) and native (n) allergenic components of endemic pollen: rBet v 1 and rBet v 2 (birch; *Betula verrucosa*), rPhl p 1 and rPhl p 5b (timothy grass; *Phleum pratense*), nArt v 1 and nArt v 3 (mugwort; *Artemisia vulgaris*). All sIgE quantifications

were performed using the ImmunoCAP technique (ThermoFisher Scientific, Uppsala, Sweden) according to the manufacturer's instructions, except for sIgE rCan s 3 that was performed using a cytometric bead array technique.⁵ Titers ≥ 0.10 kUA/L were considered positive. Recombinant Can s 3 was cloned as described elsewhere.⁶ Basophil activation tests (BAT) were performed as described in detail elsewhere.⁷ Briefly, aliquots of prewarmed heparinized whole blood were stimulated with 0.01, 0.1, 1, and 10 $\mu\text{g/mL}$ of rCan s 3. Monoclonal anti-human IgE served as a positive control (10 $\mu\text{g/mL}$, BD Biosciences, Erembodegem, Belgium), and stimulation buffer was used to measure spontaneous CD63 expression in quiescent cells. Flow cytometric analysis was performed using side scatter, anti-IgE, and CD203c to characterize the basophils. Subsequently, within this gate, the percentage of activated basophils, that is, those expressing CD63, was measured. Results were expressed as net percentages of CD63⁺ basophils after subtraction of the spontaneous expression. A BAT was considered positive if the net upregulation of CD63 was $>5\%$.⁴

Demographic data, clinical characteristics, and laboratory results are displayed in [Tables I and II](#). Both patients firmly denied any previous active use but suffered from distinct respiratory and/or mucocutaneous manifestations on passive exposure to cannabis smoke. Furthermore, both patients suffered from an oral allergy syndrome (OAS) and more generalized allergic reactions on ingestion and/or consumption of various plant-derived foods. Importantly, patient 2 reported that cannabis-related symptoms clearly preceded the onset of allergic symptoms to plant foods. As displayed in [Table II](#), the diagnosis of cannabis-related allergies and sensitization to Can s 3 was documented by skin testing, quantification of sIgE antibodies, and BAT. [Tables I and II](#) show that patient 2 displayed seasonal rhinoconjunctivitis due to a pollen allergy. However, she did not display sIgE reactivity to CCD or profilin, 2 components well known to elicit clinically irrelevant sIgE results and mimic allergy.

To summarize, here we report 2 cases in whom a cannabis allergy could have resulted from mere passive cannabis exposure, as they denied any active use of the drug. Clinical suspicion of this cannabis allergy was documented by sIgE quantification, SPT, and BAT, which, together with patients' histories, disclosed an ns-LTP syndrome. Although we cannot exclude that at least some of these food allergies result from a pre-existent pollen allergy observed in patient 2, this seems unlikely to be the sole trigger. Pollen allergy as the sole trigger seems unlikely also, because the food-related reactions in this patient frequently were more severe than traditionally observed in a pollen-related OAS that is common in our region. Alternatively, we cannot completely exclude sensitization to Can s 3 in our patients to result from cross-reactivity to other ns-LTPs. However, none of the patients reported here reported their plant-food allergies to have preceded their cannabis allergy.

In addition, patient 2 confirms that Pru p 3 cannot be considered an absolute biomarker for ns-LTP sensitization in our regions⁸ and that screening for this component might overlook a Can s 3 sensitization.

In any way, our clinical cases confirm some particularities of cannabis-related allergies that merit some attention. It is clear

TABLE I. History

Gender	Male*	Female
Age (y)	15	45
Cannabis (passive exposure)	RC, cough, wheezing	RC, D, diffuse U
Pollen	AS	RC
Plant foods (reaction(s))	Kiwi, banana, peach (OAS, U, D)	Raspberry, strawberry (AE, U, D)
Sequence of onset	1. Cannabis and fruit	1. Cannabis 2. Pollen 3. Fruit

AE, Angioedema; AS, asymptomatic; D, dyspnea; OAS, oral allergy syndrome; RC, rhinoconjunctivitis; U, urticaria.

*Patient 1 even reports to suffer cannabis-related symptoms since before the age of 8 y.

TABLE II. Results of skin prick tests, total and specific IgE, and basophil activation

Gender, age (y)	Male, 15	Female, 45
Skin prick tests (wheals, mm)		
Cannabis (LTP-rich extract)	6	9
sIgE quantification (kUA/L)		
Total IgE (kUA/L)	475	338
sIgE hemp	11.70	4.15
sIgE rCan s 3 (CBA)	0.72	19.60
sIgE rPru p 3	36.6	<0.10
sIgE rMal d 3	39.50	1.67
sIgE rAra h 9	18.60	0.45
sIgE rCor a 8	9.80	1.79
sIgE rJug r 3	10.90	1.42
sIgE nArt v 3	9.79	0.20
sIgE rPar j 2	<0.10	<0.10
sIgE rTri a 14	3.74	<0.10
sIgE rBet v 1	<0.10	0.97
sIgE rBet v 2	<0.10	<0.10
sIgE rPhl p 1	<0.10	0.46
sIgE rPhl p 5b	<0.10	0.42
sIgE nArt v 1	0.11	<0.10
sIgE bromelain	<0.10	<0.10
Basophil activation tests*		
rCan s 3 (1 µg/mL)	33%	77%

Ara h, *Arachis hypogaea*; Art v, *Artemisia vulgaris* (mugwort); Bet v, *Betula verrucosa* (birch); Can s, *Cannabis sativa*; CBA, Cytometric bead array; Cor a, *Corylus avellana*; Jug r, *Juglans regia*; LTP, lipid transfer protein; Mal d, *Malus domestica*; Par j, *Parietaria judaica*; Phl p, *Phleum pratense* (timothy grass); Pru p, *Prunus persica* (peach); sIgE, specific IgE; Tri a, *Triticum aestivum*.

*Results expressed as net % CD63 positive basophils. Normal value in 12 healthy controls below <5%.

that Can s 3-related allergies extend beyond mucocutaneous and respiratory symptoms on active use of cannabis. In essence, our case descriptions support the presumption that indirect cannabis

exposure without any previous active exposure could have caused sensitization and elicitation of allergic symptoms to cannabis together with the development of various LTP-related allergies that extend beyond the joint. Larger studies are needed to confirm these preliminary findings.

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