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Abbreviations

BAT	basophil activation test
nsLTP	non-specific lipid transfer protein
RuBisCo	Ribulose-1,5-bisphosphate carboxylase/oxygenase
SPT	skin prick test
sIgE	specific immunoglobulin E
TLP	thaumatin-like protein

Competing interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript

ABSTRACT

OBJECTIVES

Cannabis allergy has mainly been described following recreational use but some cases also point to cannabis sensitization as a result of occupational exposure. By consequence, little is known on the prevalence and clinical phenotype of occupational cannabis allergy. Therefore, this study aims at exploring the allergy associated health risks of occupational cannabis exposure in Belgian police force personnel.

METHODS

81 participants, active in the police force, reporting regular occupational cannabis exposure during the past 12 months were included. History was combined with a standardized questionnaire on allergies and cannabis exposure. BAT with a crude cannabis extract, BAT rCan s 3 and specific (s)IgE rCan s 3 as well as sIgE to house dust mite, six pollen and three mold allergens were performed.

RESULTS

Although forty-two percent of the participants reported respiratory and/or cutaneous symptoms on occupational cannabis exposure, all cannabis diagnostics were entirely negative, except in one symptomatic case demonstrating a borderline result. Furthermore, there is no significant difference between the groups with and without symptoms on cannabis exposure in terms of allergenic sensitizations.

CONCLUSIONS

The origins of the reported respiratory and cutaneous symptoms during cannabis exposure remain elusive but are probably due to non-immune reactions. It should be noted that the study was volunteer-based possibly reflecting an excessive number of symptomatic individuals Nevertheless, as only one participant reported to use fully protective gear, much improvement is to be made therein reducing the number of symptoms reported on duty, independent of their origin.

1. What is already known about this subject?

- Although rare, some anecdotal case reports and small series point to work-related cannabis allergy.
- This study aims at exploring the potential allergic health risks of occupational cannabis exposure.

2. What are the new findings?

- Respiratory and cutaneous symptoms are common in people with occupational cannabis exposure. However, IgE-mediated allergy for cannabis itself or house dust mite, molds or pollen do not seem to be the cause.
- The exact reasons for these symptoms remain elusive but are probably due to non-immune reactions.

3. How might this impact on policy or clinical practice in the foreseeable future?

- Much improvement is to be made by focusing on protective clothing possibly reducing the number of symptoms reported on duty, independent of their origin.

INTRODUCTION

Since the first report dating back to 1971(1), IgE-mediated *cannabis sativa* allergy has mainly been described in a setting of recreational (ab)use (2-9). However, some anecdotal case reports and small series also point to cannabis sensitization and allergy in a context of occupational exposure (10-16). To date, cannabis allergy has been described in cannabis growers, bird breeders, factory workers and laboratory personnel reporting both cutaneous and/or respiratory symptoms upon exposure. These reports show allergic reactivity to cannabis pollen, leaves, hemp seed and/or flower tops (9, 11-16).

Studies on recreational cannabis allergy put forward different potential allergenic components such as a thaumatin-like protein (TLP), Ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCo) and Can s 3 (the non-specific lipid transfer protein (nsLTP)). It is important to note that nsLTPs are also involved in cannabis allergy resulting from mere passive exposure to cannabis smoke and/or indirect cutaneous transmission (17).Moreover, it has been suggested that recreational cannabis allergy also displays distinct geographically dependent reactivity profiles with sensitizations to RuBisCo mostly found in the United States whereas TLP and Cans s 3 sensitizations seem to predominate in Europe (3, 4, 18-21)

A previous report on the safety of Belgian illicit indoor cannabis plantations shows that both growers and intervention staff are faced with serious health risks caused by pesticide use (22). In contrast, little is known about cannabis-associated allergies as a potential occupational health hazard, particularly in people who are involved in the dismantling of plantations on a regular basis. Actually, to the best of our knowledge, no data are available on the prevalence, clinical phenotype or the allergenic reactivity profile of these occupationally exposed individuals. Therefore, this study aims at exploring the potential allergic health risks of occupational cannabis exposure in people responsible for the localization and dismantling of illicit cannabis plantations.

METHODS

Participants

Participants were included in collaboration with the Belgian Federal Police and different Local Police departments. A research call was sent out by email as well as a poster in predesignated offices. Inclusion criteria were defined as occupational cannabis exposure during the past 12 months with cutaneous contact and/or respiratory (environmental) exposure on entering plantations or during an arrest or seizure of drugs. Individuals using oral antihistamines and/or corticosteroids, pregnant and lactating women were excluded. Demographics and history were obtained by trained physicians and complemented by a standardized questionnaire which can be found in Supplementary 1. The local ethics committee of the Antwerp University Hospital approved this study (B300201524055) and patients signed an informed consent in accordance with the Declaration of Helsinki.

Skin Prick Tests (SPT)

SPT included inhalant allergens: Birch (*Betula verrucosa*), Timothy grass (*Phleum pratense*), mugwort, (*Artemisia vulgaris*) (HAL, Haarlem, The Netherlands) and an nsLTP-rich extract from Cannabis (*Cannabis sativa*) prepared as described elsewhere (3). Skin test responses were read after 15 minutes and a wheal exceeding 3 mm (longest diameter) was considered positive. A positive control with histamine (10 mg/mL) and a negative saline control without allergen (ALK-Abello Ltd, Berkshire, United Kingdom) were performed to rule out non-responsiveness or dermographism of the skin, respectively.

Total and specific IgE measurement (sIgE)

To identify potential alternative elicitors for symptoms on occupational cannabis exposure, sIgE was quantified to house dust mite (D*ermatophagoides Pteronyssinus*), recombinant (r)Bet v 1 from birch (*Betula verrucosa*), sIgE to rPhl p 1 and rPhl p 5b from Timothy grass (*Phleum pratense*) and sIgE to mugwort (*Artemisia vulgaris*). Specific IgE to rPru p 3 from peach (*Prunus persica*) was quantified as a marker for nsLTP sensitization and sIgE to three different molds: *Cladosporium herbarum*, *Penicillium chrysogenum* and *Aspergillus fumigatus* was measured because these species were found most prevalent in illicit cannabis plantations (23, 24). Finally, total IgE was also quantified. Total and sIgE quantifications relied upon the FEIA ImmunoCAP technique (Phadia Thermo Fisher Scientific) and were carried out according to the manufacturer's instructions. For sIgE, a result $\geq$ 0.10 kU_A/L was considered positive.

Basophil activation test (BAT)

BAT was performed as described in detail elsewhere (25). Briefly, pre-warmed heparinized blood samples were stimulated with 1µg/mL of recombinant Can s 3 and 0.1µg/mL of a crude Cannabis extract. Preparation of extracts and dose-finding experiments are described elsewhere (21, 26, 27). Anti-human IgE served as a positive control (10 µg/mL, BD Biosciences, Erembodegem, Belgium) to measure cell responsiveness and stimulation buffer was used to measure spontaneous CD63 expression in quiescent cells. Analysis of basophil activation was performed using side scatter, anti-IgE and anti-CD203c to characterize the basophils. Subsequently, within the gate of $IgE^+/CD203c^+$ cells, the percentage of activated basophils, i.e. those expressing CD63, was measured. Results were expressed as net percentages of $CD63^+$ basophils, calculated by subtraction of the spontaneous expression from the allergen-induced CD63 expression. 'Responders' were defined as 15% or more CD63 basophils on stimulation with the positive control. Based on our prior validation experiments, a CD63 percentage >5% upon allergen stimulation was defined as a positive result (21, 28).

RESULTS

Study population characteristics

In total, 119 individuals responded to our research call, subsequently 87 individuals were eligible for participation in the study between February and June 2017. However, six did not receive complete diagnostic testing or were not seen by a trained physician and were therefore excluded. Of the 81 remaining participants, one participant was active in the Dutch police force; all others were part of a local or federal unit of the Belgian police force. The median age was 45.0 years (26-60 years) with a sex ratio of 56:25 males to females.

The majority (89%; 72/81) of participants report entering cannabis plantations five times a year or more, 43% (35/81) even report monthly exposure to cannabis. 53% (43/81) are actively involved in the dismantling of plantations with manual removal of the cannabis plants, the remainder enter cannabis plantations to perform forensic research, to make an inventory/supervise dismantling or are exposed to cannabis during drug arrests and/or at the police academy. Only 3/81 reported asymptomatic recreational use of cannabis dating back to more than 12 months ago. Notwithstanding recommendations only one participant reported to use of fully protective clothing.

In 17 participants (21%) a pollen allergy was confirmed by a history of seasonal

rhinoconjunctivitis combined with a positive SPT for birch, timothy grass or mugwort pollen. Three participants (4%) showed a sensitization for (at least one of the tested) molds species and 32 participants (40%) exhibited a sensitization to house dust mite. Nine participants (10%) reported atopic dermatitis (with need of topical corticosteroids in the last 12 months) and 10 participants reported asthma.

Thirty-four participants (42%) reported respiratory and/or cutaneous symptoms (up)on occupational exposure to cannabis. Thirty-three of them (97%) reported these symptoms in relation to entering cannabis plantations, the remainder experienced these symptoms when handling the drug outside of these environments. Eight individuals (10%) reported other symptoms such as headache, tiredness or facial flushing which were not specific for occupational cannabis contact. Twenty individuals reported respiratory symptoms, mainly rhinoconjunctivits (44%), throat irritation (41%) and over 40% reported mild to moderate dyspnea. Cutaneous symptoms were reported by 8 individuals and mainly comprised local or generalized pruritus and erythema. Six individuals (7%) reported both respiratory and cutaneous symptoms on exposure. When comparing the symptomatic and tolerant participants, the number of participants with asthma or atopic dermatitis did not significantly differ.

Diagnostics

Cannabis sensitization

As summarized in figure 1, 71 out of 81 participants (88%) were categorized as BAT responders. Thirty out of these seventy-one reported respiratory and/or cutaneous symptoms. In these 71 cases, all BATs for crude cannabis extract and rCan s 3 were negative, except in one symptomatic case who demonstrated an isolated and borderline result of 7% degranulating basophils (CD63 positivity) for rCan s 3. All SPT with the nsLTP rich cannabis extract yielded negative results.

Other allergic sensitizations

To identify potential alternative elicitors for the respiratory and cutaneous symptoms on occupational cannabis exposure, sIgE was quantified to house dust mite, components of different endemic pollen and three different molds. The results of these quantifications can be

found in table 1 and show that there is no significant difference between the number of sensitized patients to any of these allergens in the groups with and without respiratory and/or cutaneous symptoms on entering a cannabis plantation. Even when patients without respiratory or cutaneous symptoms are compared to each symptomatic subgroup e.g. patients with respiratory complaints, cutaneous symptoms or both, no significant differences were found.

TABLE 1: Aeroallegen diagnostics and clinical atopic features

	Respiratory and/or cutaneous symptoms?				
	ABSENT	PRESENT			
	Total n=47	Total n=34	Respiratory symptoms n=20	Cutaneous symptoms n=8	Respiratory & cutaneous symptoms n=6
Atopic dermatitis	11% (5/47)	12% (4/34)	15%	0%	17%
Asthma	11% (5/47)	12% (4/34)	15%	13%	50%
Pollen allergy[1]	15% (7/47)	30% (10/33)	30%	38%	17%
Total IgE[2]	91.4 (19.7)	93.6 (35.8)	100 (60.4)	68.3 (19.3)	107 (50.7)
sIgE house dust mite	34% (16/47)	48% (16/33)	42% (8/19)	63% (5/8)	50% (3/6)
sIgE rBet v 1	15% (7/47)	18% (6/33)	16% (3/19)	25% (2/8)	17% (1/6)
sIgE rPhl p 1	13% (6/47)	27% (9/33)	32% (6/19)	38% (3/8)	0/6
sIgE rPhl p 5b	6% (3/47)	18% (6/33)	16% (3/19)	38% (3/8)	0/6
sIgE Artemisia vulgaris	4% (2/47)	9% (3/33)	6% (1/18)	25% (2/8)	0/6
sIgE Penicillium chrysogenum	2% (1/47)	0/33	0/18	0/8	0/6
sIgE Cladosporium herbarum	2% (1/47)	0/33	0/18	0/8	0/6
sIgE Aspergillus fumigatus	2% (1/47)	0/33	0/18	0/8	0/6
sIgE rPru p 3	0/47	3% (1/33)	0/18	13% (1/8)	0/6

[1] Defined as seasonal rhinoconjunctivitis and a positive (>3mm wheal) SPT for birch, timothy or mugwort pollen. [2]Expressed as mean (standard error). p>0.05 for the comparison of the symptomatic and asymptomatic groups for all of the above-mentioned variables.

DISCUSSION

To our knowledge this is the first survey to explore the potential allergy associated health risks of occupational cannabis exposure in police forces involved in the dismantling of illegal cannabis plantations and drug arrests. Our study population consisted of participants with frequent and strong involvement in the assessment and dismantling of illegal cannabis plantations. The results demonstrate that reported respiratory and cutaneous symptoms on exposure to cannabis are common and occur mostly during or immediately after entering illegal plantations but none of the participants demonstrated an unequivocal genuine cannabis sensitization or allergy, notwithstanding the use of multiple well-standardized and validated cannabis diagnostics (3, 21). Actually, all *in vitro* and *in vivo* confirmatory tests with crude cannabis extracts and recombinant Can s 3 yield negative results except in one patient with cutaneous symptoms upon entering cannabis plantations who demonstrates an isolated and borderline basophil response to the recombinant nsLTP from cannabis. As these tests are not commercially available they were specifically manufactured and previously validated to detect a cannabis allergy (3, 21). Preliminary dose-response analyses yielded optimal allergen concentrations for the BATs which confirmed to have good performance in a larger more extensive survey (29). A small number of symptomatic patients in this current study were non-responsive in the BAT and subsequently no firm conclusions can be made about their negative BAT results for both crude cannabis extract and rCan s 3. However, false negative results are unlikely because of the negative SPT results, a test known to have a good sensitivity (3). Moreover, this study looks beyond cannabis as cause of the occupational respiratory and/or cutaneous symptoms. As a matter of fact, the prevalence of asthma, atopic dermatitis and other environmental factors that might play a role in cannabis plantations such as other traditional inhalant allergens (house dust mite, molds and pollen) were also investigated. From these analyses it appears that the reported symptoms are unlikely to be attributable to a higher prevalence in asthma or atopic dermatitis, nor other aeroallergenic causes as no differences in sensitizations were found between the symptomatic and asymptomatic individuals.

Essentially, our data indicate that the explanation for the occupation-related symptoms in our cases probably lies in alternative, non-immune mediated mechanisms. Previous studies (30, 31) have found that exposure to microbial contaminants or organic dust in hemp factory workers can attribute to byssinosis, a form of occupational asthma. Therefore, byssinosis could account to some extent for the reported respiratory symptoms but not the cutaneous

symptoms. In addition, byssinosis is mainly described in outdoor plantations whereas a report of the Belgian Science Police Office (32) mainly speak of busts of indoor plantations in this region. On the other hand, Cuypers et al. (22) recently speculated that various pesticides present in indoor plantations or sprayed on the leaves might lead to muco-cutaneous exposure and represent a health risk for intervention staff. In addition, the indoor spaces in which cannabis plantations are found, are commonly very humid and poorly ventilated. Although these explanations might explain the respiratory symptoms of dyspnea, cough and even rhinoconjunctivitis, it should be questioned whether both generalized cutaneous and respiratory symptoms, as reported in this study, are likely to be caused solely by irritation. Nevertheless, this study is the first to link these toxicities to actual health problems which makes it impossible to compare these findings to previous research.

LIMITATIONS

Collectively, our data indicate that respiratory and cutaneous symptoms are common following occupational cannabis exposure but do not originate from any of the IgE-mediated allergies tested for. However, a possible limitation of the study is that it was volunteer-based possibly causing a selection bias; people with symptoms on exposure could have been more motivated to participate in this study. Secondly, potential criticism on our study could be that the used cannabis allergy diagnostics failed to correctly document occupational cannabis sensitization. Because unlike recreational cannabis use and because of different exposition route(s), other allergens might predominate in occupational cannabis sensitization. However, as shown by our data, results obtained with BAT with a crude cannabis extract are entirely comparable with BAT rCan s 3 and SPT with an nsLTP rich extract. Actually, virtually all symptomatic participants had entirely negative explorations. Thirdly, a recent American study (33) reported that the mold *Botrytis cinerea* was found most often in outdoor cannabis plantations. This differs from the earlier findings (22, 24) concerning molds in indoor cannabis plantations, mainly in Belgium. Although this discrepancy might result from differences between indoor and outdoor environments or geographical climate differences, it would be interesting to include sIgE to *Botrytis cinerea* in future research. Finally, in future prospective research on occupational cannabis exposure, it might be beneficial to quantify urine THC levels at the time of exposure. This would enable to explore whether this occupational exposure can induce any THC uptake and enables the evaluation of subsequent physiological cannabis effects. As this study was

designed to retrospectively query occupational cannabis exposure, information on urine THC levels at the time of exposure was not available.

CONCLUSION

In conclusion, our survey confirms that respiratory and/or cutaneous symptoms are common in people with occupational cannabis exposure. However, IgE-mediated allergy for cannabis, house dust mite, molds or pollen allergy do not seem to be the causative elicitors. As a matter of fact, the exact reason(s) for these clinical manifestations remain(s) elusive but are likely due to non-immune reactions. As this study is the first study to explore the allergy associated risks to occupational cannabis exposure, its findings should be confirmed in larger studies, especially since the overall prevalence of cannabis allergy still remains elusive. A last but important fact to highlight is that only one participant reported to use fully protective gear. This observation suggests that focusing on better availability and use of protective clothing might possibly reduce the number of symptoms reported on duty, independent of their origin.

Contributorship Statement:

Decuyper I.I.: study set-up, organisation, participant inclusion, data analyses, writing of the manuscript. (guarantors of the paper)

Van Gasse A.L.: help in participant inclusion, blood sample collection and performance of skin prick tests.

Faber M.A.: discussing results, correcting and proof reading of the manuscript.

Mertens C.: performance of BAT and sIgE measurements, proof reading manuscript.

Elst J.: correcting and proof reading of the manuscript

Rihs H.P.: production of Can s 3 protein, discussing results, correcting and proof reading of the manuscript.

Sabato V.: correcting and proof reading of the manuscript.

Lapeere H.: help with participant inclusion, correcting and proof reading of the manuscript.

Hagendorens M.M.: correcting and proof reading of the manuscript.

Bridts C.H.: discussing flow-cytometric analyses, correcting and proof reading of the manuscript.

De Clerck L. S.: correcting and proof reading of the manuscript.

Ebo D.G.: help with study set-up, discussing results and analyses, writing of the manuscript, correcting and proof reading of the manuscript. (guarantors of the paper)

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FIGURES

FIGURE 1

Title: Cannabis allergy diagnostics

Footnote: from left to right: BAT with rCan s 3 (1 µg/mL) and a crude cannabis extract (0.1 µg/mL) and a skin prick test performed with an nCan s 3 rich extract (wheal>33 mm defined as a positive result). For both BATs >5%CD63-basophils was defined as a positive result. Responders are defined as ≥15% CD63-basophils after stimulation with anti-IgE, non-responders lack this feature.

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