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Allergic hypersensitivity to cannabis in patients with allergy and illicit drug users

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Abstract
Background: *Cannabis* is the illicit drug most widely used by young people in high-income countries. Allergy symptoms have only occasionally been reported as one of the adverse health effects of *cannabis* use.
Objectives: To study IgE-mediated response to *cannabis* in drug users, atopic patients, and healthy controls.
Methods: Asthmatic patients sensitised to pollen, and all patients sensitised to tobacco, tomato and latex, considered as cross-reacting allergens, were selected from a data base of 21,582 patients. Drug users attending a drug-rehabilitation clinic were also included. Controls were 200 non-atopic blood donors. Specific IgE determination, prick tests and specific challenge with *cannabis* extracts were performed in patients and controls.
Results: Overall, 340 patients, mean age 26.9 ± 10.7 years, were included. Males (61.4%) were the most sensitised to *cannabis* ($p < 0.001$). All *cannabis*-sensitised patients were alcohol users. Eighteen (72%) of the patients allergic to tomato were sensitised to *cannabis*, but a positive specific challenge to *cannabis* was highest in patients sensitised to tobacco (13/21, 61.9%), ($p < 0.001$). Pollen allergy was not a risk factor for *cannabis* sensitisation. Prick tests and IgE for *cannabis* had a good sensitivity (92 and 88.1%, respectively) and specificity (87.1 and 96%) for cannabis sensitisation.
Conclusions: *Cannabis* may be an important allergen in young people. Patients previously sensitised to tobacco or tomato are at risk. *Cannabis* prick tests and IgE were useful in detecting sensitisation.

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Introduction

It is estimated that, in 2008, more than 500,000 people received medical treatment for drug abuse in the European Union and there were almost 70,000 deaths due to overdose.[1] Symptoms often included shock, beginning with respiratory failure and skin rash. *Cannabis* use was the highest in the USA, Australia and New Zealand, followed by Europe, especially in young people.[2]

The prevalence of allergic diseases has increased progressively, with prospective studies suggesting that, between 2010 and 2020, 40%-50% of people might be affected, with rhinitis and asthma showing the greatest rising trend, and anaphylaxis being the most severe type.

The suggested risk factors for allergies include genetic predisposition, better hygiene, smoking and climate change, among others, but none explain such a large increase in so few years. Possible sensitisation to drugs has not been widely considered, as drug reactions are generally attributed to toxic causes and allergic hypersensitivity to immunological causes, with the two seen as mutually exclusive.

Our working hypothesis was that there may be allergic hypersensitivity to drugs in risk populations (atopic patients and drug abusers), as both groups have underlying immune deficiencies. *Cannabis,* which is of vegetable origin, may also sensitise people allergic to plants in the same manner as vegetal allergens.

If *cannabis* sensitisation could be detected by allergy testing, this might result in diagnostic and therapeutic advances with social, legal, and health repercussions. Adverse drug responses may not be solely toxic. Some drugs, such as penicillin or poisons derived from hymenopters,[2] are allergens for which severe hypersensitivity responses have been demonstrated. Drugs might possess vegetable allergens similar to those of pollens and plants and could provoke an immune response in predisposed people,[3–8] which could be related to toxic drug reactions, meaning the response is really a toxic-immunological mechanism. Young, productive people are affected by both types of disorder and there could be a nexus of union between them.

Objectives

The objectives of our study were to evaluate allergic hypersensitivity mediated by IgE to *Cannabis* in drug abusers and allergic patients with a possibility of cross-reactivity with *cannabis* (latex, tomato and tobacco)[8–14] and the diagnostic yield (sensitivity, specificity and predictive values) of routine tests (skin prick, specific IgE, specific challenge) in determining *cannabis* allergy as determined by bronchial response.

Patients and methods

We carried out an observational case-control study using the CONSORT guidelines, an evidence-based set of recommendations for randomised controlled trials.[10] Asthma patients of both sexes allergic to pollen and residing in Valladolid city or province who had lived in the same house from birth (ensuring that all had been exposed to similar levels of pollens, pollution and other environmental factors) and fulfilled similar clinical criteria of asthma severity were randomly selected from the registry of 21,582 patients attended in the last 20 years by the Allergy Clinic, Rio Hortega University Hospital of Valladolid, Spain.

The data on atmosphere quality were kindly provided by the excellence group on Physical Atmosphere of Valladolid University, GOA-UVA, (http://goa.uva.es). All the patients were studied by the same doctor, using standardised extracts and the same diagnostic methods.

Pollen sensitivity was defined as: a) one or more positive skin tests for pollen; b) CAP (IgE) positive > 0.35 IU/mL for pollen; or c) positive specific challenge. Asthma due to gramineae pollens was defined by prick test, specific IgE and spirometry. Lolium perenne, the most important allergen in our region, was chosen as a measurable parameter in the results of pollen tests. The reports on the pollen levels of different vegetable species in our area (kindly sent monthly to our Allergy Section from the Health Protection Service of Directorate of Public Health of our Community, www.salud.jcyl.es), have never detected *cannabis* pollen in our atmosphere.

Patients sensitised to tomato, tobacco and latex, allergens possibly implicated in cross-reactivity,[8–14] and which are contained in the same data base, were also included. These types of sensitisation are infrequent, and therefore all patients attended over the last 20 years were included in the study. Twenty-five patients sensitised to tomato, 25 sensitised to tobacco, and 18 sensitised to latex were recruited.

A group of drug-dependent patients from the Castile and Leon Association for the Aid of Drug Abusers (ACLAD) were recruited and the same tests carried out. After written informed consent was obtained, an epidemiological-clinical survey was carried out including the characteristics and origin of dependence, possible adverse reactions (by questioning close friends or relatives), potential involvement of organs and systems, emergency department (ED) care and treatment required.

The control group was comprised of 200 healthy (non-smokers, non-users of cannabis or other illicit drugs and who had never consulted the Allergy Clinic) blood donors (Blood Donation Unit, SACYL).

Cannabis consumption was self-estimated by patients as non-consumption, experimental, occasional, habitual and dependence.

The protocol was approved by Clinical Research Ethics Committees. All participants in the study gave written informed consent.

The following tests were carried out in all patients and controls:

In vivo tests

Skin tests

Skin tests, including conventional prick tests for licensed allergens using the European group protocol for the diagnosis of drug hypersensitivity,[15] included:

Allergen extracts

A standard battery of aeroallergens and foods were employed, including pollens (gramineae, trees, weeds and flowers), mites (*Dermatophagoides* and storage mites),

fungi, antigens to animals and common foods (ALK-Abelló, Madrid, Spain).

Cured tobacco extract, tomato and latex at concentrations of 1 mg/ml (Bial, Bilbao, Spain) were also included, as was extract of fresh tobacco leaf at a concentration of 1/10 weight/volume, prepared in our laboratory from uncured cured fresh leaves. Histamine 1/100 and physiological saline solution were used as positive and negative controls, respectively. Papule area was measured after 15 minutes and traced for posterior measurement by planimetry. A papule $\geq$19.62 mm^2 was considered clearly positive, corresponding to a diameter of 5 mm. This area was specified as a cut-off point after study of the ROC curves and was designed to exclude false positives due to irritation.

Preparation of cannabis extracts

The extracts used were: Fresh *Cannabis sativa* cut top leaves cold-milled and defatted with acetone (2x1; 1:5 [weight/volume] for 1 hour at 4 °C), and after drying, extracted with 0.1 mol/L Tris-HCl pH 7.5, 10 mM EDTA (1:5 [weight/volume] for 1 hour at 4 °C). After centrifuging at 9000 g for 30 minutes at 4 °C, the supernatant was dialysed against H_2O (cut-off point, 3.5 kd) and lyophilised. This extract was used both for bronchial challenge and skin tests.

Diagnostic and pulmonary function tests

Baseline diagnostic spirometry was carried out in all participants.

Specific bronchial *cannabis* challenge was carried using the Chai technique with modifications as previously described.[12] *Cannabis* extracts were diluted to 0.005 mg/mL, 0.05 mg/mL, 0.5 mg/mL, 1 mg/mL and 5 mg/mL. After full stop titration according to Gleich's technique with extract of fresh *cannabis* leaf, the dilution that provoked a papule of 7 mm^2 was determined. This dilution was the initial dose used for the bronchial challenge carried out in consenting patients and controls (141 as whole).

In ACLAD patients, direct *inhalatory challenge* tests were performed after inhalation of a *cannabis* cigarette, with forced spirometry at 5, 10 and 15 minutes. After baseline spirometry, challenge was carried out if FEV1 was > 80%. For *cannabis* extract challenge, two millilitres of the extract were introduced in the dosimeter and the patient breathed normally for two minutes. Spirometry was carried out and repeated at 5, 10 and 15 minutes. If there was no change in FEV1 or if the reduction was > 10%, the next higher concentration was used until a reduction in FEV1 $\geq$ 20% was achieved, which was considered a positive bronchial challenge. If the reduction in FEV 1 was near 15%, the patient was instructed to inhale the next higher dilution for one minute only. Late responses were monitored with a Mini Wright peak flow meter at 2, 6, 12, and 14 hours after the test, and the best measurement of three chosen. *Cannabis* extract and tobacco challenges were also performed in consenting controls.

In vitro tests

Specific IgE

Specific IgE was determined for a battery of aeroallergens and foods: wheat, barley and rye, milk, alpha-lactalbumin, beta-lactoglobulin, casein, egg white and yolk, fish, and vegetables (vegetables, legumes, nuts, fresh fruit) tobacco, latex and tomato, using the ImmunoCAP System (Phadia, Uppsala, Sweden). Levels of IgE > 0.35 kU/L were considered positive. Biotiniled *Cannabis* extracts were coupled to Streptavidin-ImmunoCAP solid phase (Streptavidin-ImmunoCAP, Phadia AB. Uppsala, Sweden), according to Sander et al. (2005).[16] Specific IgE to Cannabis was determined by the ImmunoCAP System using the above mentioned solid-phases.

Statistical analysis

The association between study variables was analysed using Pearson's Chi^2 test. When the number of cells with expected levels > 5 was > 20%, they were calculated using Fisher's exact test or the likelihood ratio test.

The Student's t test for independent samples was used to compare means and when the number of groups to compare was greater, the ANOVA test was used. When these were not applicable, the non-parametric Mann-Whitney U test (for two groups) or Kruskal Wallis H test (for more than two groups) were used.

Statistical significance was established as $p < 0.05$ and 95% confidence intervals (CI) were calculated as necessary.

The statistical analysis was made using the SPSS version 15.0 programme.

Results

Global description of the sample

One hundred and sixty-eight patients and 200 controls were initially recruited: of these 28 patients were lost to the study and 140 were finally analysed.

Table 1 shows baseline characteristics of the study groups.

Fifty-five (36.4%) patients had attended the ED, most-commonly for asthma (70.7%), urticaria (19.3%), and anaphylaxis (16.4%). Other frequent allergic symptoms were tomato intolerance (with oral syndrome, 35.7%) and rhinitis. Twenty-six patients (18.6%), suffered from rhinitis. In all cases rhinitis was associated with asthma.

Seventy-four (53.2%) patients had positive skin tests for *cannabis*, 48 (34.3%) had *cannabis*-specific IgE and 30% (42 patients) positive bronchial challenge. This would seem to indicate that only 56.7% of positive patients with skin test had positive *cannabis* challenge, although there may have been positive *cannabis* prick tests due to cross-reactivity with tomato, latex or tobacco.

The percentage of patients with positive tobacco prick test (37%) was more concordant with positivity of tobacco-specific IgE (44.5%). The same was observed in patients sensitive to tomato (positive prick test 31.2%, positive IgE 34.1%).

Table 1 Baseline characteristics of study patients.

Variable	All	Tomato	Pollen	Tobacco	Latex	ACLAD	Sig.
Patients recruited	168	25	40	25	18	50	
Completers (n = 140)	140	n = 25(17.9%)	n = 34(24.3%)	n = 21(15.0%)	n = 18(12.9%)	n = 42(30.0%)	
Age (years)	26.9 ± 10.7	22.84 ± 6.9	22.2 ± 10.2	23.7 ± 7.8	21.8 ± 7.3	36.9 ± 8.9	
Sex (female)	54	9	15	7	14	9	
Occupation							
Student	76 (54%)	20 (80%)	30 (88.2%)	14 (66.7%)	12 (66.7%)	0	<0.001
Housewife	12 (8.6%)	4 (16%)	2 (5.9%)	5 (23.8%)	1 (5.6%)	0	
Unemployed	19 (13.6%)	0	0	0	0	19 (45.2%)	<0.001
Other	33 (23.6%)	1 (4%)	2 (5.9%)	2 (9.5%)	5 (27.8%)	23 (54.8%)	
Smoking	62.9%	16 (64%)	10 (29.4%)	21 (100%)	2 (11.1%)	39 (92.9%)	<0.001
Age of initiation (mean)	16.0 ± 3.5	16.1 ± 2.6	17.2 ± 5	17.2 ± 4.8	17.5 ± 0.7	14.9 ± 2.1	NS
Years (mean)	13.4 ± 10.8	7.1 ± 5.8	6.1 ± 6.5	7.0 ± 7.3	8.5 ± 10.6	21.6 ± 9.5	<0.001
Consumption of							
Alcohol	108 (77.1%)	19 (76%)	16 (47.1%)	21 (100%)	11 (61.1%)	41 (97.6%)	<0.001
Legal stimulants	120 (85.7%)	25 (100%)	21 (61.8%)	19 (90.5%)	14 (77.8%)	41 97.6%)	<0.001
Clinical symptoms							
Atopy		25 (100.0%)	34 (100.0%)	21 (100.0%)	18 (100.0%)	29 (69.0%)	<0.001
Asthma		18 (72.0%)	34 (100.0%)	21 (100.0%)	8 (44.4%)	18 (42.9%)	<0.001
Rhinitis		0 (0.0%)	14 (41.2%)	1 (4.8%)	0 (0.0%)	11 (26.2%)	<0.001
Anaphylaxis		9 (36.0%)	0 (0.0%)	4 (19.0%)	4 (22.2%)	6 (14.3%)	0.001
Urticaria		5 (20.0%)	1 (2.9%)	2 (9.5%)	10 (55.6%)	9 (21.4%)	<0.001
Oesophagitis		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
SAO		24 (96.0%)	0 (0.0%)	8 (38.1%)	3 (16.7%)	15 (35.7%)	<0.001
Tomato intolerance		24 (96.0%)	0 (0.0%)	11 (52.4%)	3 (16.7%)	15 (35.7%)	<0.001
Emergency department		4 (16.0%)	0 (0.0%)	12 (57.1%)	3 (16.7%)	31 (73.8%)	<0.001

Drug consumption and allergy tests (positive *cannabis* prick test area, positive bronchial challenge and specific IgE) of study patients are shown in Table 2.

None of the tests performed in the 200 blood donor volunteers were positive for cannabis.

Differences by groups

Clinical differences between groups are shown in Table 3.

Aclad patients

Thirty-one patients had attended the ED, six (14.3%) due to anaphylaxis; 18 (42.9%) due to asthma; and nine (21.4%) due to urticaria-angio-oedema. Fifteen (35.7%) also had oral syndrome with raw tomato, but had only excluded tomato from the diet without medical consultation.

Other dependence. Other drugs used included alprazolam (33.33%) and other stimulants in 41 (97.6%) patients. One patient was on insulin.

Twelve patients had HAV, 7 VHB, 13 HCV, and 6 HIV. One patient suffered latex-related nocturnal asthma cured by change of latex mattress.

Of all the asthmatics, 12 presented altered respiratory function tests (obstructive spirometry) at baseline. All patients had a positive bronchial challenge for *cannabis*.

Patients allergic to tomato

Cannabis. Eight (44%) had used *cannabis* experimentally only once, nine (50%) occasionally, one habitually, and there was no drug abuser.

In 13 patients (61.9%) with positive IgE and prick test, *cannabis* challenge was positive and all admitted *cannabis* use.

Four (16%) had attended the ED after smoking *cannabis* and drinking alcohol: two with asthma, one with anaphylaxis and one with oral angio-oedema.

No patient tolerated tomato but all tolerated other *Solanaceae*. Twenty-four (96%) suffered oral syndrome after eating raw tomato.

Patients allergic to gramineae pollen

Cannabis. Three were experimental users and one occasional. There was no habitual or dependent user.

Thirty-one patients tolerated tomato normally. The most frequent disorders were spring asthma (100%) and urticaria (one patient). None had anaphylaxis or angio-oedema or had attended the ED.

Patients allergic to tobacco

Cannabis. Seven patients were experimental and five were occasional users, with no habitual or dependent user.

Nine (45%) tolerated tomato without oral discomfort and 11 (52%) were intolerant, of whom eight had oral allergy syndrome. Nine (52.85%) were positive for both tests.

The 12 patients sensitised to *cannabis* had attended the ED, four due to anaphylaxis (after a party at which *cannabis*, tobacco and alcohol were consumed) and eight due to asthma. All were occasional consumers.

Table 2 Drug consumption and allergic tests in study patients.

Variable	All n = 140	Pollen	Tomato	Tobacco	Latex	ACLAD	Sig.
Allergy tests							
Positive cannabis prick test	74 (53.2%)	5 (14.7%)	23 (92%)	15 (75%)	8 (44.4%)	24 (58.5%)	<0.001
Positive cannabis specific IgE	48 (34.3%)	3 (8.8%)	17 (68%)	12 (57.1%)	2 (11.1%)	14 (33.3%)	<0.001
Positive cannabis bronchial challenge	42(30%)	0	13 (52%)	13 (61.9%)	1 (5.6%)	15 (35.7%)	<0.001
Cannabis user (Yes/No)	85 (60.7%)	4 (11.8%)	18 (72%)	12 (57.1%)	9 (50%)	42 (100%)	<0.001
Age initiation	17.0 ± 3.6	14.5 ± 1	16.5 ± 2.9	18.6 ± 6.1	17.7 ± 2.7	16.8 ± 3.1	NS
Mean years consumption	12.2 ± 10.4	1 ± 0	3.3 ± 2.2	6.2 ± 5.2	8.3 ± 6.1	19.7 ± 9.4	<0.001
Self-estimated ever cannabis consumption	68 (48.5%)	0	12 (48%)	10 (47.6%)	4 (22.22%)	42 (100%)	
Never	48 (34.28)	30 (88.2%)	6(24%)	5 (23.8%)	7 (38.9%)	0 (0%)	<0.001
Experimental	26 (18.6%)	3 (8.8%)	8 (44%)	5 (23.8%)	9 (50%)	0 (0%)	<0.001
Occasional	22 (15.7%)	1 (2.9%)	9 (50%)	10 (47.6%)	2 (11.1%)	0 (0%)	<0.001
Habitual	2 (1.4%)	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	<0.001
Dependence	42 (30%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	42 (100%)	<0.001
Tobacco	88 (62.9%)	10 (29.4%)	16 (64%)	21 (100%)	2 (11.1%)	39 (92.9%)	<0.001
Age initiation	16 ± 2.6	17.2 ± 5	16.1 ± 2.6	17.2 ± 4.8	17.5 ± 0.7	19.7 ± 9.4	NS
Mean years consumption	13.4 ± 10.8	6.1 ± 6.5	7.1 ± 5.8	7 ± 7.3	8.5 ± 10.6	21.6 ± 9.5	<0.001
Cocaine	39 (27.9)%,	0 (0%)	1 (4%)	1 (4.8%)	0 (0%)	37(88.1%)	<0.001
Age initiation (yrs)	17.5 ± 2.5	0	17	20	0	17.4 ± 2.5	NS
Mean years consumption	12.2 ± 10.4	0	1	18	0	19.1 ± 8.9	0.001
Heroin	31 (22.1%)	0	0	0	0	31 (73.8%),	<0.001
Age initiation	18.1 ± 3.1	0	0	0	0	18.1 ± 3.1	
Mean years Consumption	18.1 ± 3.1 years	0	0	0	0	20.4 ± 8.4	
Methadone	21 (15%)	0	0	0	0	21 (50%),	<0.001
Age initiation	33.7 ± 8.5	0	0	0	0	33.7 ± 8.5	
Mean years consumption	3.9 ± 2.4	0	0	0	0	3.9 ± 2.4	
Amphetamines	15 (10.7%)	0	0	2 (9.5%)	0	33.42%),	<0.001
Benzodiazepines	25 (17.9%)	0	0	1 (4.8%)	0	24(57.1%)	<0.001
Legal stimulants	120 (85.7%)	25 (100%)	21 (61.8%)	19 (90.5%)	14 (77.8%)	41 (97.6%)	NS

The main disorders were asthma in 21 patients, urticaria in two (9.5%) and anaphylaxis four (19%).

Patients allergic to latex

Cannabis. Seven were experimental users and none was a dependent user.

Three patients were tomato intolerant and three (16.7%) had attended the ED (all users of *cannabis*, after one night of partying) one due to asthma and two due to anaphylaxis.

Differences by type of consumption

Table 5 shows positive prick and IgE test in study patients.

Greater *cannabis* consumption was associated with smoking and consumption of cocaine, heroin and alcohol ($p < 0.001$). Anaphylaxis and ED attendance ($p < 0.001$) was observed in experimental and occasional users. (Table 4)

The highest levels of positive *cannabis* prick tests and specific IgE were observed in habitual and dependent users

Table 3 Differences in clinical variables according to study group.

Variable	Tomato n = 25	Pollen n = 34	Tobacco n = 21	Latex n = 18	ACLAD n = 42	Sig.
Atopy	25 (100.0%)	34 (100.0%)	21 (100.0%)	18 (100.0%)	29 (69.0%)	<0.001
Asthma	18 (72.0%)	34 (100.0%)	21 (100.0%)	8 (44.4%)	18 (42.9%)	<0.001
Rhinitis	0 (0.0%)	14 (41.2%)	1 (4.8%)	0 (0.0%)	11 (26.2%)	<0.001
Anaphylaxis	9 (36.0%)	0 (0.0%)	4 (19.0%)	4 (22.2%)	6 (14.3%)	0.001
Urticaria	5 (20.0%)	1 (2.9%)	2 (9.5%)	10 (55.6%)	9 (21.4%)	<0.001
Oesophagitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
OAS	24 (96.0%)	0 (0.0%)	8 (38.1%)	3 (16.7%)	15 (35.7%)	<0.001
Tomato Intol.	24 (96.0%)	0 (0.0%)	11 (52.4%)	3 (16.7%)	15 (35.7%)	<0.001
Emergency department	4 (16.0%)	1 (2.9%)	12 (57.1%)	3 (16.7%)	31 (73.8%)	<0.001

OAS: Oral allergy syndrome. Intol: Intolerance.

Table 4 Differences in clinical variables according to level of cannabis consumption.

Variable	Non consumer n = 48	Experimental Consumer n = 26	Occasional Consumer n = 22	Habitual Consumer n = 2	Dependence n = 42	Sig.
Atopy	48 (100.0%)	26 (100.0%)	22 (100.0%)	2 (100.0%)	29 (69.0%)	<0.001
Asthma	42 (87.5%)	19 (73.1%)	18 (81.8%)	2 (100.0%)	18 (42.9%)	<0.001
Rhinitis	14 (29.2%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	11 (26.2%)	<0.001
Anaphylaxis	2 (4.2%)	6 (23.1%)	8 (36.4%)	1 (50.0%)	6 (14.3%)	0.006
Urticaria	9 (18.8%)	8 (30.8%)	1 (4.5%)	0 (0.0%)	9 (21.4%)	NS
OAS	8 (16.7%)	15 (57.7%)	11 (50.0%)	1 (50.0%)	15 (35.7%)	0.004
Tomato Intol.	8 (16.7%)	15 (57.7%)	13 (59.1%)	2 (100.0%)	15 (35.7%)	<0.001
Emergency department	0 (0.0%)	7 (26.9%)	11 (50.0%)	2 (100.0%)	31 (73.8%)	<0.001

OAS: Oral allergy syndrome. Intol: Intolerance.

($p < 0.001$). There were no differences between experimental and occasional users in the positivity of tests. There were no significant differences in the number of positive results according to the type of consumption (Table 5).

Yield of diagnostic tests

In study patients, the *cannabis* prick test had the highest sensitivity (92.7%) but a lower specificity, due to cross-reactivity with vegetable allergens, while specific IgE had a sensitivity of 88.1% and a specificity of 88.8%.

If controls (none of whom were positive for *cannabis* prick test, IgE, or challenge) were included, prick test sensitivity remained equal, but specificity increased, while IgE sensitivity and specificity remained high. (Table 6)

Interpretation of the results

1. After ACLAD patients, the highest level of use of addictive substances was in patients allergic to tobacco ($p < 0.001$). However, the group with the highest level of sensitisation according to the prick test and specific IgE were patients allergic to tomato ($p < 0.001$), although patients allergic to tobacco had the highest level of positive *cannabis* challenge ($p < 0.001$), suggesting cross-sensitisation to *cannabis* and tomato and also that there may be true sensitisation to *cannabis* and false sensitisation due to cross-reactivity in patients sensitised to tomato.
2. In addition to patients allergic to tomato, a greater or lesser degree of tomato intolerance was observed in half the patients allergic to tobacco and 15/42 ACLAD patients, all with positive *cannabis* challenge.
3. The area of the *cannabis* prick test was greater in ACLAD patients ($p < 0.001$) but levels of *cannabis*-specific IgE were higher in patients allergic to tomato ($p < 0.001$).
4. Intolerance to tomato should lead to the suspicion of *cannabis* consumption ($p < 0.001$).
5. Neither the severity of the clinical profiles nor ED admission was related to the level of consumption, with occasional users also being a risk group.
6. Both the prick test and specific IgE were efficient in detecting sensitisation to *cannabis* and positivity was related to severe clinical profiles (anaphylaxis, asthma, angio-oedema) requiring ED admission.

Table 5 Differences in positive prick (area$\geq$19 mm^2) and IgE ($\geq$0.35kU/L) tests according to level of cannabis consumption.

Variable	Non consumer	Experimental Consumer	Occasional Consumer	Habitual Consumer	Dependence	Sig.
Prick lolium	36/48 (75.0%)	20/26 (76.9%)	17/22 (77.3%)	1/1 (100.0%)	10/41 (24.4%)	<0.001
IgE lolium	41/48 (85.4%)	22/26 (84.6%)	19/22 (86.4%)	2/2 (100.0%)	9/22 (40.9%)	0.001
Prick cannabis	14/48 (29.2%)	16/26 (61.5%)	18/22 (81.8%)	2/2 (100.0%)	24/41 (58.5%)	<0.001
IgE cannabis	8/48 (16.7%)	11/26 (42.3%)	13/22 (59.1%)	2/2 (100.0%)	14/42 (33.3%)	0.002
Chall. cannabis	0/48 (0.0%)	10/26 (38.5%)	15/22 (68.2%)	2/2 (100.0%)	15/42 (35.7%)	<0.001
Prick						
tomato	6/48 (12.5%)	13/26 (50.0%)	12/22 (54.5%)	1/1 (100.0%)	11/41 (26.8%)	<0.001
IgE tomato	7/48 (14.6%)	14/26 (53.8%)	13/22 (59.1%)	1/1 (100.0%)	12/41 (29.3%)	<0.001
Prick						
tobacco	8/48 (16.7%)	9/26 (34.6%)	18/22 (81.8%)	2/2 (100.0%)	14/40 (35.0%)	<0.001
IgE tobacco	10/48 (20.8%)	9/26 (34.6%)	19/22 (86.4%)	2/2 (100.0%)	13/21 (61.9%)	<0.001
Prick latex	13/48 (27.1%)	13/26 (50.0%)	16/22 (72.7%)	2/2 (100.0%)	8/42 (19.0%)	<0.001
IgE latex	13/48 (27.1%)	13/26 (50.0%)	17/22 (77.3%)	2/2 (100.0%)	6/24 (25.0%)	<0.001

Chall: Challenge.

Table 6 Sensitivity, specificity, positive and negative predictive values, false positives and false negatives of cannabis tests.

	Cannabis Prick		Cannabis IgE	
Variable	Value	95% CI	Value	95% CI
Study patients only				
Sensitivity	92.7	83.5-100.0	88.1	77.1-99.1
Specificity	63.3	53.2-73.3	88.8	82.0-95.5
PPV	51.3	39.3-63.4	77.1	64.1-90.0
NPV	95.4	89.5-100.0	94.6	89.4-99.7
False positives	36/139 (25.9%)		11/140 (7.9%)	
False negatives	3/139 (2.2%)		5/140 (3.6%)	
Study patients and healthy controls				
Sensitivity	92.7	83.5-100.0	88.1	77.1-99.1
Specificity	87.1	82.9-91.2	96.0	93.6-98.5
PPV	51.3	39.3-63.4	77.1	64.1-90.0
NPV	98.8	97.2-100.0	98.2	96.4-99.9
False positives	36/319 (11.3%)		11/320 (3.4%)	
False negatives	3/319 (0.9%)		5/320 (1.6%)	

Prick area $\geq$19mm2 and IgE$\geq$0.35kU/L versus positive bronchial challenge test.
PPV: Positive predictive area.
NPV: Negative predictive area.

Discussion

It is estimated that in 2008 *cannabis* was consumed by 3.9% of the world population aged 15-64 years.[17] Recent epidemiological studies[2] show that regular *cannabis* use in adolescence causes adverse effects, including dependence syndrome, respiratory and cardiovascular alterations, increased traffic accidents, and alterations in psychosocial development and mental health. The possible adverse allergic effects have been very infrequently studied.

Isolated cases of allergic hypersensitivity to *Cannabis sativa* have been described, including rhinoconjunctivitis due to inhalation of *cannabis* pollen,[3] urticaria and contact dermatitis due to handling of *cannabis* plants,[4,5] and anaphylaxis due to *cannabis* ingestion.[6] Paradoxically, the protective action of *cannabis* against allergies has also been described.[7] Cross-reactivity between *cannabis* and tomato allergens[8] and skin lesions due to inhalation of *cannabis* have been reported.[9]

Allergic hypersensitivity to tobacco has been demonstrated by our group in a large series of patients.[11,12] *Cannabis* challenge was positive in 52% of our patients sensitised to tomato and 61% sensitised to tobacco and both seem to be risk factors for *cannabis* sensitisation. ED admissions were due to severe symptoms related to probable multidrug consumption. Patients with anaphylaxis were allergic to tomato and tobacco. Patients not attending the ED in spite of severe symptoms were younger ($p < 0.001$) and possibly trying to hide their behaviour.

Might *cannabis* be an allergen?

Reported cases are anecdotal and related to *cannabis* pollen inhalation. There are no reports of allergic hypersensitivity in drug abusers, who are normally excluded from clinical trials or studies, and usually receive no care for allergies, which are considered a minor problem. We felt a large study to highlight this health problem was warranted. This clinical study is based on routine allergy techniques, but we hope future studies will include new techniques of allergen analysis and cross-reactivity based on molecular biology and array techniques. The main strength of our study is that there is little attention in the literature to allergy associated with *cannabis*, even though about 4% of the population use this drug.

ED admissions for *cannabis* consumption have quadrupled in the last decade, from 7.4% to 28%.[1,2] However, *cannabis* consumption has decreased by 6.8% since 2004.[17] Drug abusers are usually attended by primary health care centres and drug rehabilitation centres and are rarely referred to outpatient allergy clinics but often admitted to the ED. The adverse effects of drug consumption are often not stated by intoxicated patients.

Once the possibility of allergic sensitisation to drugs is considered, new routes of laboratory detection of drug seem possible even when there is no current consumption, as the allergic reaction lasts over time and can be detected by specific antibodies. This simple, sensitive and objective method could have important social, legal and therapeutic repercussions:

1. **Social repercussions**: Explaining that patients have an allergic reaction to the drug that may worsen progressively could be another argument in persuading them to reject drugs.
2. **Legal repercussions**: Drug consumption could be detected even when there is no current consumption as the antibodies can be detected for some years.
3. **Therapeutic repercussions**: In addition to avoiding fatal cases of anaphylaxis, specific immunotherapy, which is highly efficient for toxic allergens such as hymenopter toxins, may be possible. If the allergenic epitopes coincided with A-9-tetrahydrocannabinol (THC), specific immunotherapy against these allergens might be

possible, using blocking antibodies which, theoretically, would annul the effect of the drug by blocking cannabinoid receptors and achieving tolerance to the allergen, presumably resulting in reduced consumption. The greater diagnostic yield obtained with *cannabis* bud extracts, which contain the greatest concentration of THC, would support this theory.

Strikingly, we found considerable *cannabis* consumption in a randomly-selected group of allergic patients. Studies in the USA have found that 10% of people who have ever consumed *cannabis* end up consuming it daily[1] and, therefore, the risk of experimental consumption, especially in young students, should not be underestimated. According to our results, smokers and patients with difficulties ingesting tomato are also at risk. Although tomatoes possess allergens with cross-reactivity with *cannabis* allergens, 72% of patients with tomato allergy admitted *cannabis* consumption and the 13 patients with positive challenge had symptoms when they smoked it. Smokers sensitised to tobacco also responded to challenge with pure extract of *cannabis* leaf, showing that not only tobacco provoked their symptoms. Of the ACLAD patients, who had the highest rates of smoking, and consumption of alcohol and other drugs, 29/42 patients had atopy, an incidence greater than in the general public. Alcohol is reported to increase atopy and sensitisation to allergens.[18]

The effect of *cannabis* on pulmonary function is not clear.[16] Habitual users have more symptoms of bronchitis and respiratory infections. *Cannabis* does not seem to increase the risk of emphysema[19,20] and obstructive patterns improved in some of our patients after smoking *cannabis*. An Arizona study[21] showed that 70% of atopic patients responded to marijuana pollen skin test, a habitual contaminating pollen in Arizona that provokes asthma, rhinitis and urticaria in sensitised patients, suggesting the opportunity for specific immunotherapy. However, there are few later references to possible *cannabis* allergy[2–8] or specific immunotherapy.

We found the prick test highly-sensitive, although the diagnostic yield was due to a high negative predictive value. The papule area (19 mm^2, diameter 5x5 mm), eliminated more false positives, improving the AOC. Specific IgE determination is a highly-sensitive and specific diagnostic parameter, with a better positive predictive value, and could be an easy, cheap and useful way of determining current or past contact with *cannabis*, and might one day be used for medical and legal ends (traffic accidents, behavioural alterations, violence).

In conclusion, *cannabis* consumption may be associated with a measurable allergic response. Determination of *cannabis*-specific IgE is a rapid, inexpensive method with high sensitivity and specificity that could detection consumption, sensitisation and possible allergy to *cannabis* and, perhaps, other illicit drugs.

Conflict of interest

The authors report no conflict of interest.

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