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Allergy in Children to Illicit Drugs, Tobacco and Alcohol

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ABSTRACT

Background: *Illicit drugs, tobacco, and alcohol contain allergens that can trigger, inadvertently affecting children living with consumer relatives.*

Objective: *This real-life study is aimed to evaluate the presence of sensitization to illicit drugs (cannabis, opium derivatives, and cocaine), tobacco, and allergens derived from alcoholic beverages in children.*

Methods: *Children (0-14 years) with severe allergic symptoms and domestic exposure to drugs, tobacco, or alcohol were included. Prick, specific IgE, molecular analysis, and Dot Blot assays were performed. We tested 46 aeroallergens and food, pure cocaine, coca leaf extract, opium, Papaver somniferum seeds, cannabis, tomato, tobacco, latex, malt, hops, and lipid transfer proteins (LTPs) from grapes.*

Results: *Of the 150 selected patients, 134 completed the study. Among them, 10 tested positive for cocaine, 21 for cannabis, 6 for opioids, 18 for tobacco, 9 for latex, 17 for malt, 13 for hops, and 12 for grape LTPs. A significant association was found between drug, tobacco, and alcohol exposure and the development of severe allergic symptoms ($p < 0.001$). Specific relationships were observed: cocaine ($p < 0.009$) and tobacco ($p < 0.05$) were associated with severe asthma. Malt and cannabis sensitization ($p < 0.001$) were linked to anaphylaxis, with additional associations found for hops ($p < 0.003$) and grape LTP ($p < 0.006$). Molecular assays revealed binding of the IgE from these paediatric patients to the tested samples.*

Conclusions: *Atopic children may be considered at risk of developing hypersensitivity to allergens from illicit drugs, tobacco, and alcohol. This possibility should not be underestimated.*

Keywords

Illicit drugs, Children, Cannabis, Marijuana, Opium, Heroin, Cocaine, Tobacco, Alcohol, Latex, Malt, Hops, Beer, Wine, Lipid-transfer proteins, LTP, Illicit drug allergy.

Abbreviations

IgE: Immunoglobulin E, CAP: Immunoassay ImmunoCAP® Allergen, SACYL: Health Department of Castile and Leon Community, CRD: Component resolved diagnosis.

Declaration of all sources of funding

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Introduction

Recent reports on illicit drug use in various countries have highlighted important changes in consumption patterns. The increase in the use of certain drugs stands out mainly cannabis,

heroin, cocaine, amphetamines, and newly designed synthetic drugs.

It is possible that the adverse reactions to drugs are not solely due to toxicity. Illicit drugs are pharmacologically active substances, similar to penicillin or hymenoptera venoms, which are known allergens that can cause severe hypersensitivity responses. Interestingly, drugs, tobacco, and alcoholic beverages contain plant allergens like those found in pollens and other plants, which may also trigger allergic reactions in predisposed individuals [1-9].

There is a possibility that immune responses and toxicity are interconnected, and that the body reacts through a combined toxic-immunological mechanism. The young population is particularly affected by both allergy and drug dependence, raising the question of a potential link between these conditions. Our research team has explored this in various publications over recent years [1-8].

With the rising social, medical, and occupational exposure to Cannabis, there has been growing interest in its allergens. In collaboration with German and Belgian researchers, we recently described a recombinant allergen derived from the RNA of *Cannabis sativa* leaves (spp. sativa cv. Kompolti) [6]. This allergenic extract has proven useful in diagnosing cannabis allergy.

In another study, we used extracts of *Papaver somniferum* obtained from the seeds of opium capsules to diagnose allergies to heroin and other opioids. This facilitated the early detection of allergies to analgesics and anaesthetics derived from opium before surgery [5-7].

We have also identified allergens in coca leaves and detected cases of allergic reactions to local anaesthetics derived from cocaine, leading to national and European patents [8,9].

Aside from accidental drug exposure at home, passive smoking is a serious problem for children. Tobacco is a significant source of plant allergens, particularly lipid transfer proteins (LTPs), which are highly allergenic and can cross-react with latex [9].

When children present with allergic symptoms, we usually test for common environmental and food allergens. However, we rarely suspect sensitization to drug, tobacco, or alcohol-related allergens in children under 14. This gap in diagnosis prompted us to begin focused research on this vulnerable population.

Methods

Trial Oversight

We conducted a real-life cross-sectional observational study with both retrospective and prospective data. Our Hospital Ethics Committee reviewed and approved the protocol (Ref. No. CEIm PI030-20). Informed consent from the parents of participating children and from the children themselves when they were of consenting age was obtained.

Patients

We included children aged 0 to 14 years, randomly selected from those attending our Allergy Clinic with significant allergy symptoms (rhinitis, severe perennial conjunctivitis, asthma, or anaphylaxis), where exposure to drugs, tobacco, or alcohol at home was suggested in the anamnesis. We followed CONSORT 2010 guidelines [9].

As controls, we included 20 patients with multiple allergies to illicit drugs (cocaine, heroin, and cannabis) diagnosed through skin tests, specific IgE, and positive challenge tests, recruited from the drug addiction support association ACLAD. Additionally, five patients with asthma and confirmed tobacco allergy, diagnosed using the same techniques, were included.

For negative controls, we selected 50 healthy donors who were non-smokers, did not consume illicit drugs or alcoholic beverages, and had previously tested negative in all allergy assessments.

If parents refused skin prick testing (SPT) of their children with drug allergens, an alternative option was offered using cross-reactive allergens: tomato LTP for cannabis, *Papaver somniferum* seed extract for opium derivatives, and coca tea or mepivacaine for cocaine.

We also conducted an anonymous and voluntary survey about lifestyle habits (smoking, alcohol consumption, and drug use), ensuring confidentiality and professional secrecy for all collected data.

In addition to SPT with 46 aeroallergens and food, we included the following extracts: pure cocaine, coca leaf, mepivacaine, opium, *Papaver somniferum* seeds, cannabis, tomato, tobacco, latex, malt, and hops. The selection of these allergens was based on their relevance in previous studies, as they were found to be the most frequent allergens in drug-dependent populations [1-9].

Allergen Extracts

We used a standard battery of aeroallergens and food allergens, including pollens (from grasses, trees, weeds, and flowers), mites (*Dermatophagoides* and storage mites), fungal spores, animal antigens, common food allergens, and peach, wheat, grape, and tomato (*Lycopersicon esculentum*) LTP. All allergens were supplied by INMUNOTEK and ALK-Abelló, Madrid, Spain.

Drug Extracts and Protein Quantification

Protein extracts from the different drugs were prepared by grinding and incubating the samples in PBS at 2–8°C for 16 hours. Following incubation, the samples were centrifuged for 10 minutes. The supernatant was filtered with decreasing pore sizes until 0.2 µm. Protein quantification was performed using the Bio-Rad Protein Assay kit based on the Bradford method [10].

Dot Blot Assay for Detection of Specific IgE

The **Dot Blot assay** was performed using the **Bio-Dot Microfiltration Apparatus** (Bio-Rad, Hercules, CA). For Western

Blot, the proteins were transferred to a nitrocellulose membrane, incubated overnight with the patient's serum and serum from a non-allergic patient as a negative control treated with a 1:2000 dilution of mouse anti-human IgE for 1 hour before visualizing the bands using chemiluminescence.

A **nitrocellulose membrane** was pre-hydrated with **Tris-Buffered Saline** and mounted onto the apparatus. Serial dilutions of the samples were prepared and were allowed to passively filter through the dots.

We incubated the membrane for 1 hour with the patient's sera and then it was treated with a 1:3000 dilution of mouse anti-human IgE for 1 hour before visualizing the bands by chemoilluminescence.

Results

Of the 150 patients initially selected, **134 completed the study.** The participants were divided into three groups: **50 healthy controls, 53 breastfeeding children** whose primary sensitizer was cow's milk, and **31 older children** with severe allergy symptoms (such as asthma or anaphylaxis), randomly selected from those whose parents provided consent. Finally, **29 patients withdrew** from the study.

The mean age in the **cow's milk allergy group** was **2.1 ± 1 years**, with **77% male participants**, while the mean age of the **31 children with severe symptoms** was **7.3 ± 3.3 years**, with **58.1% male participants.**

In the cow's milk allergy group, 7 patients (13.2%) had eosinophilic esophagitis, and 3 (5.7%) were diagnosed with severe asthma. Among the 31 children with severe allergic symptoms, 8 (25.8%) were diagnosed with severe asthma, defined by frequent hospital admissions and poor response to treatment. Ten children (32.3%) experienced anaphylaxis, 6 of whom tested positive for LTPs.

Allergen sensitization, using prick tests and specific IgE measurements, was tested. In the cow's milk allergy group, 7 patients (13.2%) were sensitized to cannabis, 7 (13.2%) to tobacco, 5 (9.4%) to malt and hops, 4 (7.5%) to grape LTP, 3 (5.7%) to cocaine, and 2 (3.8%) to latex. In the group of 31 children with severe allergic symptoms and potential home exposure to drugs, tobacco, or alcohol, 14 (45.2%) were sensitized to cannabis, 12 (38.7%) to malt, 11 (35.5%) to tobacco, 10 (32.3%) to hops, 10 (32.3%) to cocaine, 6 (19.4%) to latex, and 3 (9.7%) to opioids Table 1.

These findings suggest a high prevalence of sensitization to both environmental and drug-related allergens in children with severe allergy symptoms, particularly in those with potential home exposure to these substances.

The difference in sensitization between the groups was highly significant. The consumption of drugs, tobacco, and/or alcohol was strongly associated with the symptoms developed by children, showing a highly significant relationship (**$p < 0.001$**) for allergens from cocaine, cannabis, tobacco, and alcoholic beverages. The association was weaker for opioids and non-significant for mepivacaine (Table 2).

Regarding the relationship between severe symptoms and specific allergens, a significant association was observed between sensitization to cocaine (**$p < 0.009$**) and tobacco (**$p < 0.05$**) with severe asthma. For anaphylaxis, a strong relationship was found with sensitization to cannabis and malt (**$p < 0.001$**), while lower but still significant associations were observed with hops (**$p < 0.003$**) and grape (**$p < 0.006$**) (Table 3).

Table 1: Allergens implicated in selected patients and controls.

	Controls N= 50	Milk allergy N = 53	Sig.*	Severe allergic symptoms N = 31	Sig.*	Sig.**
Cocaine Prick	0 (0,0%)	2 (3,8%)	0,496	10 (32,3%)	<0,001	0,001
Cocaine IgE	0 (0,0%)	3 (5,7%)	0,243	7 (22,6%)	0,001	0,034
Opium Prick	0 (0,0%)	3 (5,7%)	0,243	3 (9,7%)	0,053	0,665
Opioids IgE	0 (0,0%)	3 (5,7%)	0,243	3 (9,7%)	0,053	0,665
Cannabis Prick	0 (0,0%)	7 (13,2%)	0,013	10 (32,3%)	<0,001	0,036
Cannabis IgE	0 (0,0%)	7 (13,2%)	0,013	14 (45,2%)	<0,001	0,001
Tobacco Prick	0 (0,0%)	7 (13,2%)	0,013	12 (38,7%)	<0,001	0,007
Tobacco IgE	0 (0,0%)	7 (13,2%)	0,013	11 (35,5%)	<0,001	0,016
Mepivacaine Prick	0 (0,0%)	1 (1,9%)	0,999	0 (0,0%)	0,999	0,999
Mepivacaine IgE	0 (0,0%)	0 (0,0%)	0,999	1 (3,2%)	0,383	0,369
Latex Prick	0 (0,0%)	2 (3,8%)	0,496	8 (25,8%)	<0,001	0,004
Latex IgE	0 (0,0%)	3 (5,7%)	0,243	6 (19,4%)	0,002	0,070
Malt Prick	0 (0,0%)	4 (7,5%)	0,118	13 (41,9%)	<0,001	<0,001
Malt IgE	0 (0,0%)	5 (9,4%)	0,057	12 (38,7%)	<0,001	0,001
Japanese hop Prick	0 (0,0%)	5 (9,4%)	0,057	9 (29,9%)	<0,001	0,020
Japanese hop IgE	0 (0,0%)	3 (5,7%)	0,243	10 (32,3%)	<0,001	0,003
Grape LTP Prick	0 (0,0%)	2 (3,8%)	0,496	8 (25,8%)	<0,001	0,004
Grape LTP IgE	0 (0,0%)	4 (7,5%)	0,118	8 (25,8%)	<0,001	0,028

Table 2: Relation with home habits in parents and relatives (drinking alcohol and smoking tobacco and/or drugs.

	No drink N= 111	Drinking N = 23	Sig.*	No smoking N = 100	Smoking N = 26	Sig.
Cocaine Prick	3 (2,7%)	9 (39,1%)	<0,001	3 (3,0%)	9 (34,6%)	<0,001
Cocaine IgE	3 (2,7%)	7 (30,4%)	<0,001	3 (3,0%)	7 (26,9%)	0,001
Opioids Prick	1 (0,9%)	5 (21,7%)	0,001	1 (1,0%)	5 (19,2%)	0,001
Opioids IgE	1 (0,9%)	5 (21,7%)	0,001	1 (1,0%)	5 (19,2%)	0,001
Cannabis Prick	1 (0,9%)	16 (69,6%)	<0,001	1 (1,0%)	16 (61,5%)	<0,001
Cannabis IgE	2 (1,8%)	19 (82,6%)	<0,001	1 (1,0%)	20 (76,9%)	<0,001
Tobacco Prick	4 (3,6%)	15 (65,2%)	<0,001	1 (1,0%)	18 (69,2%)	<0,001
Tobacco IgE	4 (3,6%)	14 (60,9%)	<0,001	1 (1,0%)	17 (65,4%)	<0,001
Mepivacaine Prick	0 (0,0%)	1 (4,3%)	0,172	0 (0,0%)	1 (3,8%)	0,206
Mepivacaine IgE	0 (0,0%)	1 (4,3%)	0,172	0 (0,0%)	1 (3,8%)	0,206
Latex Prick	0 (0,0%)	10 (43,5%)	<0,001	0 (0,0%)	10 (38,5%)	<0,001
Latex IgE	0 (0,0%)	9 (3971)	<0,001	0 (0,0%)	9 (34,6%)	<0,001
Malt Prick	0 (0,0%)	17 (73,9%)	<0,001	0 (0,0%)	17 (65,4%)	<0,001
Malt IgE	1 (0,9%)	16 (69,6%)	<0,001	0 (0,0%)	17 (65,4%)	<0,001
Japanese hop Prick	0 (0,0%)	14 (60,9%)	<0,001	0 (0,0%)	14 (53,8%)	<0,001
Japanese hop IgE	1 (0,9%)	12 (52,2%)	<0,001	1 (1,0%)	12 (46,2%)	<0,001
Grape LTP Prick	0 (0,0%)	10 (43,5%)	<0,001	0 (0,0%)	10 (38,5%)	<0,001
Grape LTP IgE	0 (0,0%)	12 (52,2%)	<0,001	0 (0,0%)	12 (46,2%)	<0,001

Table 3: Relationship between severe symptoms and implicated allergen.

	No Asthma N= 123	Asthma N = 11	Sig.*	No Anaphylaxis N = 124	Anaphylaxis N = 10	Sig.
Cocaine Prick	8 (6,5%)	4 (36,4%)	0,009	10 (8,1%)	2 (20,0%)	0,221
Cocaine IgE	7 (5,7%)	3 (27,3%)	0,036	9 (7,3%)	1 (10,0%)	0,552
Opioids Prick	7 (5,7%)	3 (27,3%)	0,036	9 (7,3%)	1 (10,0%)	0,552
Opioids IgE	5 (4,1%)	1 (9,1%)	0,408	5 (4,0%)	1 (10,0%)	0,378
Cannabis Prick	14 (11,4%)	3 (27,3%)	0,147	11 (8,9%)	6 (60,0%)	<0,001
Cannabis IgE	17 (13,8%)	4 (36,4%)	0,071	14 (11,3%)	7 (70,0%)	<0,001
Tobacco Prick	15 (12,2%)	4 (36,4%)	0,050	14 (11,3%)	5 (50,0%)	0,005
Tobacco IgE	14 (11,4)	4 (36,4%)	0,042	14 (11,3%)	4 (40,0%)	0,029
Mepivacaine Prick	1 (0,8%)	0 (0,0%)	0,999	1 (0,8%)	0 (0,0%)	0,999
Mepivacaine IgE	1 (0,8%)	1 (4,3%)	0,999	0 (0,0%)	1 (10,0%)	0,075
Latex Prick	7 (5,7%)	3 (27,3%)	0,036	6 (4,8%)	4 (40,0%)	0,003
Latex IgE	9 (4,9%)	3 (27,3%)	0,027	7 (5,6%)	2 (20,0%)	0,136
Malt Prick	13 (10,6%)	4 (36,4%)	0,034	11 (8,9%)	6 (60,0%)	<0,001
Malt IgE	14 (11,4%)	3 (27,3%)	0,147	11 (8,9%)	6 (60,0%)	<0,001
Japanese hop Prick	11 (8,9%)	3 (27,3%)	0,091	11 (8,9%)	3 (30,0%)	0,071
Japanese hop IgE	10 (8,1%)	3 (27,3%)	0,075	9 (7,3%)	4 (40,0%)	0,008
Grape LTP prick	8 (6,5%)	2 (18,2%)	0,192	6 (4,8%)	4 (40,0%)	0,003
Grape LTP IgE	10 (8,1%)	2 (18,2%)	0,256	8 (6,5%)	4 (40,0%)	0,006

In patients sensitized to cannabis, **93%** responded to **Can s 3**, **67%** to **tomato LTP (Lyc e 3)**, **57%** to **tobacco LTPs**, **21%** to **CCD (nAna c 2)**, **29%** to **grass allergens (Lol p 1)**, **25%** to **nCyn d 1**, and **20%** to **peach LTP (Pru p 3)**, which is the primary sensitizer in LTP allergy in the Mediterranean area. Cross-inhibition tests using **Can s 3**, **Pru p 3**, and **Lyc e 3** demonstrated that **Can s 3** was the primary sensitizer. Although tomatoes contain allergens cross-reactive with *Cannabis sativa* allergens, **86%** of the parents of children with tomato allergy admitted to having cannabis at home.

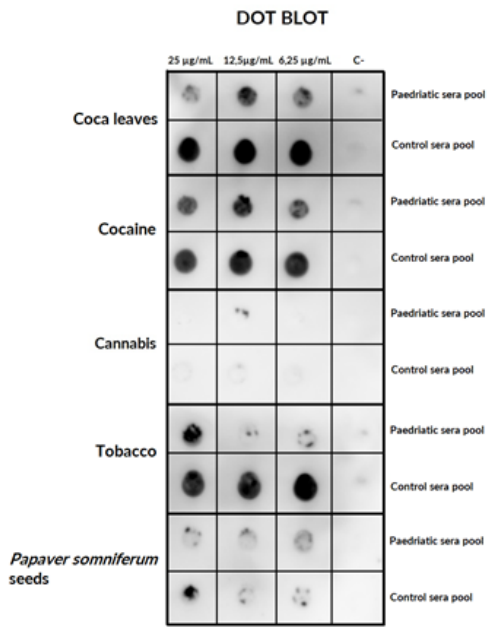
A significant relationship between the intensity of the Dot Blot reaction and specific IgE levels was confirmed. The study compared Dot Blot results with specific IgE levels in 31 patients (Table 4), allowing the identification of individual allergic reactivity patterns. Differences between patients were observed in the intensity of IgE responses, suggesting variability in sensitization. Some patients demonstrated reactivity to multiple substances, indicating the possibility of cross-allergies.

Figure 1

IgE dot blot. Each dot represents the allergenic study sample (coca tea, cocaine, cannabis, tobacco leaves and opium seeds. The intensity of the dot is directly proportional to the binding of IgE from the serum pool to the study sample.

Table 4: Specific IgE (ELISA and DOTblot): A: Cocaine, B: Opium, C: Tobacco, D: Malt, E: Hop, F: Beer.

	Specific IgE					IgE DOTblot			
	A	B	C	D	E	A	B	C	F
1	0.64	0.39	1.6	2.4	100.0	+++			
2	0.14	0.02	0.06	0.0	0.1				
3	0.23	0.16	0.15	0.1	0.1	+++			
4	0.25	0.23	0.95	1.4	3.1		++		++
5	0.04	0.01	0.04	0.0	0.0				
6	0.01	0.01	0.05	0.0	0.0	++	++		++
7	0.12	0.12	0.67	1.07	2.35	++		+++	
8	0.93	0.65	13.4	5.94	2.46	+			
9	0.42	0.68	3.11	3.86	10.1	+	+		
10	0.1	0.02	0.04	0.02	0.03				
11	0.09	0.07	0.43	0.04	0.06			++	+++
12	0.2	0.02	0.0	0.03	0.07				
13	0.06	0.07	0.02	0.03	0.02	+	+++		+
14	0.53	0.02	0.21	0.1	0.06	+		+++	++
15	0.06	0.07	0.86	0.1	0.78				
16	0.03	0.01	0.01	0.01	0.01			++	
17	0.11	0.14	0.11	0.0	0.14		+		+
18	0.03	0.01	0.58	0.23	0.03		+		
19	0.06	0.02	0.03	0.02	0.01				
20	0.1	0.1	0.37	0.01	0.02		++		
21	0.03	0.01	0.02	0.09	0.0			+++	+++
22	0.25	0.01	0.17	0.3	2.03			+++	+++
23	0.24	0.01	0.08	0.35	0.08		+++		+
24	0.24	0.01	0.15	0.58	1.47				
25	0.21	0.01	0.14	0.21	0.06			++	+++
26	0.3	0.01	0.35	0.36	0.31	+++			
27	0.44	0.01	0.01	0.07	0.0	+++			
28	0.14	0.02	0.51	0.66	0.42	++			
29	0.26	0.01	0.23	0.78	0.12	+++	+++		++
30	0.29	0.01	0.23	0.76	0.69	+			
31	0.38	0.01	0.11	0.28	0.01	++	+		



In summary, the key findings were:

- Variable intensity of reactivity was observed between different samples and patients.
- Allergic responses were identified to the following allergens:
  - **Tobacco leaves** and **opium seeds** → Strong IgE binding
  - **Cocaine** and **beer** → Moderate reactivity
  - **Cannabis** and **coca tea** → Less intense or absent reactivity

Discussion

This manuscript describes clinical cases of children presenting with severe allergic hypersensitivity symptoms, such as asthma and anaphylaxis, not explained by routine allergy tests. Due to the young age of the patients, allergic symptoms caused from illicit drugs, tobacco, or alcoholic beverages, were not suspected as potential causal agents. However, this hypothesis emerged after a more comprehensive allergy evaluation [1,2,8].

Our line of investigation began in 2008, following the case of an 11-year-old boy who experienced weekend anaphylaxis caused

by cannabis exposure. This case prompted research into allergic sensitization to illicit drugs and revealed a high prevalence of this clinical problem among teenagers, especially given that cannabis is the most commonly used illegal drug among young people.

We explored the possibility of allergic sensitization to drugs, demonstrating that these reactions are not solely due to toxic effects. The immune response and drug toxicity may be interconnected, with the body reacting through a combined toxic-immunological mechanism. Drugs of abuse contain allergens that can provoke an immune response. This includes not only regular users but also experimental, accidental, and occasional users, such as adolescents exposed at home through parental or family use.

To successfully conclude this study, multicentric cooperation was essential, including the **University of Valladolid**, **University of the Basque Country**, **Río Hortega Hospital**, **Association to Help Drug Addicts (ACLAD)**, **Government Delegation and Local Police**, as well as **INMUNOTEK** laboratories. A multidisciplinary team of specialists participated in the project, comprising allergists, pediatricians, immunologists, toxicologists, and other professionals.

In recent years, the **peptide sequence of the main cannabis allergen**, LTP, was identified [3-6]. This allergenic extract has proven useful in the **diagnosis and prevention of cannabis allergy [2,3,10].**

Additionally, extracts of *Papaver somniferum*, obtained from the seeds of the opium capsule, to diagnose **opioid allergy** to analgesics and anaesthetics derived from opium were used [4]. Further studies were conducted on the **possible allergens present in alcoholic beverages**, expanding our knowledge of allergic responses in this context [11,12].

In our study, **tobacco** and ***Papaver somniferum* seeds** were identified as the most potent allergens, indicating that the proteins present in these substances can trigger significant immune responses in children with atopic predisposition. **Cocaine** and **beer** also showed sensitization in some individuals, which may be associated with passive exposure in the home environment.

We found that **21 children responded to cannabis**, specifically to allergens from the plant's buds, predominantly from the *Cannabis sativa* variety. In all cases, the children's families occasionally smoked cannabis at home. All the children with positive test results had parents who were active smokers.

Marijuana is the most widely used illicit drug worldwide. While its active components, **Δ9-tetrahydrocannabinol (THC)** and **cannabidiol (CBD),** are well known, there is a growing trend toward **decriminalization and legalization** of its use based on its therapeutic potential as an **antispasmodic, analgesic, anxiolytic, and antiemetic**. It is used also to treat **drug-resistant epilepsy** (none of the children in this study had this condition).

However, **cannabis use remains risky**, particularly in households where small children live. Occasional use at home poses significant risks if the drug is left within reach of children, who may handle it or inhale it accidentally.

The **adverse effects of cannabis** can greatly reduce the quality of life in children. For children with allergies, especially those sensitized to LTPs, accidental exposure can cause severe allergic reactions, including **anaphylaxis**, which can be life threatening.

Inhalation of **cannabis cigarette smoke** and **gastrointestinal consumption** can induce **conjunctival injection, rhinitis, asthma, and anaphylaxis [9]**. In the long term, cannabis exposure can cause **bronchial lesions** and **bronchoconstriction** leading to asthmatic symptoms [13,14]. Several studies on occupational exposure in cannabis plantations have also reported **skin reactions**, including **urticaria and eczema [15,16]**.

In our study, we identified a child who experienced **anaphylaxis** after ingesting a **cannabis cupcake**, further highlighting the risk of gastrointestinal exposure to cannabis in allergic individuals.

We identified **10 children with hypersensitivity to cocaine** (*Erythroxylum coca* and *Erythroxylum novogranatense*). Cocaine can be consumed orally, sublingually, intravenously, intramuscularly, or subcutaneously. Sensitized children could have accidentally **inhaled or ingested cocaine powder**. In these cases, **severe asthma** was detected, and **fatal asthma exacerbations** have been reported in the literature. Other serious manifestations such as **urticaria and angioedema** [8,20-23] have also been described. The adulterants commonly found in cocaine, such as **lidocaine** and **levamisole**, can pose additional risks [24,25].

In our experience, **coca leaf extract** provides better diagnostic yield and clinical safety compared to potentially adulterated cocaine powder. It has also proven useful in diagnosing **allergy to local anaesthetics derived from cocaine** [8,26].

We also identified **6 children with opioid sensitivity**, with the **most likely route of exposure being the ingestion of cough syrups containing codeine**. We ruled out prior anaesthesia as a source of exposure. In these cases, it is critical to distinguish **IgE-mediated allergy** to opium derivatives from **non-specific histamine release reactions**. Historically, syrups containing opium in paediatric patients were commonly used, but their use has been discontinued in recent years.

In our study**, skin tests** using the **oil fraction of *papaver* seeds** was more reproducible and allowed testing in children whose parents did not consent to heroin testing.

There are many causes of **adverse reactions to alcohol [30-38]**, which children can accidentally have consumed.

Alcohol itself can trigger **anaphylaxis**, although most allergic reactions are caused by allergens in **wine** and **beer**. These include

lipid transfer proteins (LTPs) from grapes, which are present in wine, and LTPs from cereals (barley, wheat, rye, and corn), used in the production of malt and hops in beer [34,35]. **Omega-5 gliadin**, found in wheat, can also cause **anaphylaxis** when combined with physical exercise (*wheat-dependent exercise-induced anaphylaxis*, WDEIA), and was tested in component-resolved diagnostics (CRD). Reactions caused by **Saccharomyces spp.** are extremely rare, although we included **yeast** in the allergen panel. **Hymenoptera venom** contamination in wine has been reported in some cases, but none was detected in our samples. However, **wine fining agents** such as **ovalbumin, lysozyme, cow's milk, casein, and fish gelatin** can pose risks for children sensitized to this foods [37-40].

Contact with **ethanol** may cause **dermatitis**, worsen **urticaria,** and trigger **rosacea** flares [30-38]. None of these latter symptoms were observed in our study population, but **anaphylaxis** was the most significant clinical finding associated with alcohol exposure.

Our study confirmed **allergic hypersensitivity to illicit drugs, tobacco, and alcohol** in children passively exposed at home. We detected **specific IgE reactivity** against proteins present in **tobacco, *papaver* seeds, cocaine, and beer**, highlighting the potential for **cross-sensitization** between these substances, which could broaden the spectrum of allergies in affected children.

Given the **increasing social and medical exposure to drugs and alcohol**, and the possibility of **domestic exposure**, there may be a rise in the frequency of allergic reactions, even in young children. These reactions, must be detected as early as possible, due to their potential severity. **Early clinical suspicion** can help prevent undesirable clinical outcomes in this highly vulnerable population.

Further studies are required to evaluate the **clinical manifestations** of these sensitizations and their **long-term impact**.

Currently, **strict avoidance** of these substances remains the only effective therapeutic measure. In conclusion, **children especially atopic children and those with LTP hypersensitivity must be considered at risk of developing hypersensitivity to illicit drugs, tobacco, and alcohol**. We should not be overlooked or underestimated this possibility.

References

1. Armentia A, Castrodeza J, Ruiz-Muñoz P, et al. Allergic hypersensitivity to cannabis in patients with allergy and illicit drug users. Allergol Immunopathol (Madr). 2011; 39: 271-279.
2. Armentia A, Martín B, Herrero M, et al. Molecular diagnosis in cannabis allergy. J Allergy Clin Immunol Pract. 2014; 2: 351-352.
3. Hans-Peter Rish, Alicia Armentia, Wolfram Lobin, et al. IgE binding properties of a recombinant lipid transfer protein from cannabis sativa (rCan s 3). Annals of Allergy Clin immunol. 2014; 113: 233-42014.
4. Armentia A, Pineda F, Palacios R.y cols, et al. Utility of opium seed extract tests in preventing hypersensitivity reactions during surgery. Allergol Immunopathol (Madr). 2014; 42: 56-63.
5. Rish AP, Armentia A, Lobin W, et al. A recombinant lipid transfer protein from cannabis sativa: IgE binding properties in patients with symptoms to cannabis. Clinical and translational Allergy. 2014; 4: 57-58.
6. Armentia A, Pineda F, Martín-Armentia B, et al. A useful method to detect opioid allergies. J Allergy Clin Immunol Pract. 2015; 3: 829-830.
7. Armentia A, Martín-Armentia B, Martín-Armentia S, et al. Cocaine Allergy in Drug-Dependent Patients and Allergic People. J Allergy Clin Immunol Pract. 2018; 6: 201-207.
8. Decuyper II, Armentia A, Martín-Armentia B, et al. Reactions to Illicit Drugs (Marijuana, Opioids, Cocaine) and Alcohol. Allergy Clin Immunol Pract. 2021; 9: 3006-3014.
9. David Moher, Sally Hopewell, Kenneth F Schulz, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reportind parallel gropup randomized trials. Int J Surg. 2019; 340: c869.
10. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem. 1976; 72: 248-254.
11. Alicia Armentia, Fernando Pineda, Sara Fernández. Wine-induced anaphylaxis and sensitization to hymenóptera venom. N Engl J Med. 2007; 16: 357: 791-820.
12. Caballero I, Aqut M, Armentia A, et al. Importance of tetrahydroiso alpha-acids to the microbiological stability of beer. J AOAC Int. 2009; 92: 1160-1164.
13. Yacukka S. Endocannabinoids in tje retina: from marijuana to neuroprotection. Pro Retin Eye Res. 2008; 27: 501-526.
14. ZeigerJS, Silvers WS, Winders TA, et al. Cannabis attitudes and patterns of use among followers of the Allergy & Asthma Network. Ann Allergy Asthma Immunol. 2021; 126: 401-410.
15. Decuyper II, Van Gasse A, Faber MA, et al. Occupational cannabis exposure and allergic risks. Occup Environ Med. 2019; 76: 78-82.
16. Willians C, Thompstone J, Wilkinson M. Work related contact urticaria to Cannabis sativa. Contact dermatitis. 2008; 58: 62-63.
17. Gamboa P, Sanchez-Monge R, Sanz ML, et al. Sensitization to cannabis sativa caused by a novel allergenic lipid tranfer protein Can s3. J Allergy Clin Immunol. 2007; 120: 1459-1460.
18. Decuyper II, Rish HP, Mertens CH, et al. A new cannabis allergen in Northwestern Europe: the oxigen-evolving enhancer protein 2 (OEEP2). J Allergy Clin Immunol Pract. 2020; 8: 2421-2424.
19. Faber MA, Sabato V, Bridts CH, et al. Clinical relevance of the Hevea brasiliensis lipid transfer protein Hev b 12. J Allergy Clin Immunol. 2015; 135: 1645-1648.

20. Self TH, Shah SP, March KL, et al. Asthma associated with the use of cocaine, heroin, and marijuana: A review of the evidence. J Asthma. 2017; 54: 714-722.
21. Ettinger NA, Albin RJ. A review of the respiratory effects of smoking cocaine. Am J Med. 1989; 87: 664-668.
22. Underner M, Perriot J, Peiffer G, et al. Asthma and cocaine use. Rev Mal Respir. 2019; 36: 610-624.
23. Castro-Villamor MA, de las Heras P, Armentia A, et al. Cocaine-induced severe angioedema and urticaria. Ann Emerg Med. 1999; 34: 296-297.
24. Ribeiro M, Trevizol Ap, Frajzinger R, et al. Adulterants in crack cocaine in Brazil. Trends Psychiatry Psychotjer. 2019; 41: 186-190.
25. Brunt TM, van der Berg J, Pennings E, et al. Adverse effects of levamisole in cocaines users: a review and risk assessment. Arch Anaesth. 2019; 29: 892-900.
26. Stepanovic B, Sommerfield D, Lucas M, et al. An update on allergy and anaphylaxis in pediatric anesthesia. Paediatr Anaesth. 2019; 29: 892-900.
27. Caron AB. Allergy to multiple local anesthetics. Allergy Asthma Proc. 2007; 28: 600-601.
28. Jussi L, Lammintausta K. Sources of sensitization, cross-reactions, and occupational sensitization to topical anaesthetics among general dermatology patients. Contact Dermatitis. 2009; 60: 150-154.
29. Armentia A, Pineda F, Martin-Armentia B, et al. Endophthalmitis related to lemon allergy in a heroin addict. Allergol Immunopathol (Madr). 2016; 44: 472-474.
30. Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health. 2007; 30: 5-13.
31. Edenberg HJ, McClintick JN. Alcohol Dehydrogenases, Aldehyde Dehydrogenases, and Alcohol Use Disorders: A Critical Review. Alcohol Clin Exp Res. 2018; 42: 2281-2297.
32. Gross ER, Zambelli VO, Small BA, et al. A personalized medicine approach for Asian Americans with the aldehyde dehydrogenase 2*2 variant. Annu Rev Pharmacol Toxicol. 2015; 55: 107-127.
33. Matsumura Y, Stiles KM, Reid J, et al. Gene Therapy Correction of Aldehyde Dehydrogenase 2 Deficiency. Mol Ther Methods Clin Dev. 2019; 15: 72-82.
34. Quercia O, Zoccatelli G, Stefanini GF, et al. Allergy to beer in LTP-sensitized patients: beers are not all the same. Allergy. 2012; 67: 1186-1189.
35. Picariello G, Mamone G, Cutignano A, et al. Proteomics, peptidomics, and immunogenic potential of wheat beer (Weissbier). J Agric Food Chem. 2015; 63: 3579-3586.
36. Morita E, Yamamura Y, Mihara S, et al. Food-dependent exercise-induced anaphylaxis: a report of two cases and determination of wheat-gamma-gliadin as the presumptive allergen. Br J Dermatol. 2000; 143: 1059-1063.
37. Bansal RA, Tadros S, Bansal AS. Beer, Cider, and Wine Allergy. Case Reports Immunol. 2017; 7958924.
38. Kirschner S, Belloni B, Kugler C, et al. Allergenicity of wine containing processing aids: a double-blind, placebo-controlled food challenge. J Investig Allergol Clin Immunol. 2009; 19: 210-217.
39. Vassilopoulou E, Karathanos A, Siragakis G, et al. Risk of allergic reactions to wine, in milk, egg and fish-allergic patients. Clin Transl Allergy. 2011; 1: 10.
40. Meyer P, Zanetti S. Detection of Traces of Ovalbumin and Casein in White and Red Wines by Quantitative Western Blotting. J Food Sci. 2015; 80: 2102-2109.