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Cannabis allergy: what do we know anno 2015

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List of abbreviations

Act d	*Actinidia deliciosa* (kiwi fruit)
Ara h	*Arachis hypogaea* (peanut)
ATP	adenosine triphosphate
BAT	basophil activation test
Bet v	*Betula verrucosa* (birch)
Can s	*Cannabis sativa*
CCD	cross-reactive carbohydrate determinants
Cit s	Citrus sinensis (tangerine)
Cor a	*Corylus avellana* (hazelnut)
CRD	component resolved diagnosis
Cup a	*Cupressus arizonica* (cypress native to the southwest of north America)
Hev b	*Hevea brasiliensis* (natural rubber tree)
Jug r 3	Juglans regia (walnut)
Lyc e	Lycopersicom esculentum (tomato)
Mal d	*Malus domestica* (apple)
Mus a	*Musa acuminate* (banana)
Ns-LTP	non-specific lipid transfer protein
OAS	oral allergy syndrome
Phl p	*Phleum pratense* (Timothy grass)
PRP	pathogenesis-related protein
Pru av	*Prunus avium* (cherry)
Pru p	*Prunus persica* (peach)
RuBisCo	ribulose-1,5-biphosphate carboxylase/oxygenase
sIgE	specific immunoglobulin E
THC	tetrahydrocannabinol
TLP	thaumatin-like protein
Tri a	Triticum aestivum (wheat)
Vit v	Vitis vinifera (grape)

Abstract

For about a decade, IgE-mediated cannabis (marihuana) allergy seems to be on the rise. Both active and passive exposure to cannabis allergens may lead to a cannabis sensitization and/or allergy. The clinical manifestations of a cannabis allergy can vary from mild to life-threatening reactions, often depending on the route of exposure. In addition, sensitization to cannabis allergens can trigger various secondary cross-allergies, mostly for plant-derived food. This clinical entity, which we have designated as the "cannabis-fruit/vegetable syndrome" might also imply cross-reactivity with tobacco, latex and plant-food derived alcoholic beverages. These secondary cross-allergies are mainly described in Europe and appear to result from cross-reactivity between non-specific lipid transfer proteins (ns-LTPs) or thaumatin-like proteins (TLPs) present in *Cannabis sativa* and their homologues that are ubiquitously distributed throughout plant kingdom. At present, diagnosis of cannabis-related allergies rests upon a thorough history completed with skin testing using native extracts from buds and leaves. However, quantification of specific IgE antibodies and basophil activation tests (BAT) can also be helpful to establish correct diagnosis. In the absence of a cure, treatment comprises absolute avoidance measures including a stop of any further cannabis (ab)use.

Key words: allergy, cannabis, prevalence, Can s 3, cross-reactivity, diagnosis, IgE, CD63, basophil activation

Introduction

"Cannabis" is a generic term for various preparations [marihuana (or weed), hashish, hashish oil] that are obtained from *Cannabis sativa* (order: Rosales, family *Cannabaceae*) that contain elevated levels of cannabinoids, particularly delta 9-tetrahydrocannabinol (THC); several of them being psychoactive substances. Although, for the time being, cannabis use is still illegal in most countries, it is increasingly and ubiquitously used for its relaxing or euphoric effects, especially by adolescents and young adults. When used, derivatives of dried flowers and subtending leaves mostly from the female plant (marihuana) and preparations derived from resinous extract (hashish) are consumed by smoking, vaporizing, chewing or ingestion.

Prevalence

Although several reports on occupational cutaneous and respiratory allergies to different members of the *Cannabaceae* family like industrial hemp and hop (*Humulus lupulus)* have been published (Spiewak et al., 2001, Williams et al., 2008, Herzinger et al., 2011), descriptions of genuine IgE-dependent allergic reactions in drug abusers remain rare. This under-reporting probably results from the illegal status of cannabis use, which makes the patients reluctant to admit their abuse. The first description dates from 1971 and reports a 29-year-old house wife who suffered from an allergic reaction after smoking a marihuana cigarette. Diagnosis of cannabis allergy was established by positive scratch testing and passive transfer studies (Liskow et al., 1971). Today, no information is available about the prevalence of IgE-mediated cannabis allergy but it is likely cannabis allergy to be an increasing problem since a few years.

Routes of exposure and sensitization

As regards cannabis, various routes of exposure and sensitization that can all lead to primary cannabis allergy exist and have been described. First, people may be exposed to cannabis through active use by smoking, vaporizing, chewing, ingestion or intravenous use of the drug. Secondly, cutaneous contact could be a possible route of sensitization. This could be important in cannabis growers and police men seizing cannabis plantations. An alternative route of sensitization could be passive exposure by proxy when allergens become airborne or are transferred via contact. Therefore, also (young) children can be exposed to cannabis allergens, e.g. through smoking by parents and/or siblings (Ebo et al., 2013b).

It should also be kept in mind that *C. sativa* is an anemophilous plant that produces wind-borne pollen in case of a male plant. These pollen, once airborne, can be transported over extreme long distances (Freeman, 1983, Stokes et al., 2000, Torre et al., 2007, Mayoral et al., 2008, Singh and Shahi, 2008, Prasad et al., 2009). For example, in Nebraska, where industrial *C. sativa* is cultivated, *C. sativa* pollen account for 36% of the total pollen count during mid- to late-August (Stokes et al., 2000). In European countries such as France (Anselme et al., 2011), Spain (Mayoral et al., 2008) and Italy (Torre et al., 2007), similar observations were made. As only female (non-pollinating) plants are cultivated for illicit use, it is unlikely abusers of cannabis, who grow their own plants, to become sensitized to marihuana through pollen.

Finally, secondary cannabis allergy might result from cross-reactivity with allergenic compounds such as non-specific lipid transfer proteins (ns-LTPs) or thaumatin-like proteins (TLPs) present in other plants from closely or more distantly related origin (Larramendi et al., 2013).

Cannabis allergens

To date, the allergenic composition of *Cannabis sativa* remains relatively elusive. Larramendi *et al*. (Larramendi et al., 2013) described six different bands with a molecular weight of 10, 14, 20, 35, 38 and 60-kDa that were recognized by the individual patients' sera. The 10-kDa IgE binding band was already described in other reports (Gamboa et al., 2007, de Larramendi et al., 2008, Tanaka et al., 1998) and probably corresponds to Can s 3, the ns-LTP of *C. sativa* (Gamboa et al., 2007) that belongs to the pathogenesis-related proteins (PRP)-14 group (Van Loon, 1999). In a study by Armentia *et al* (Armentia et al., 2014), sensitization to the purified cannabis ns-LTP was observed in 124 out of 130 patients (95.3%) with a primary cannabis allergy.

The 38-kDa band corresponds with a TLP, which belongs to the PRP-5 family (Larramendi et al., 2013). Although in the study of Larramendi *et al.* (Larramendi et al., 2013) no homology was found between the 14-kDa band and any known allergen, this band probably corresponds with a profilin (de Larramendi et al., 2008).

In a study of Nayak *et al*. (Nayak et al., 2013), 23-kDa and 50-kDa seem to be the most prominent bands, even after deglycosylation, meaning the IgE-binding epitopes not to reside in the carbohydrate moiety of the glycoprotein allergens. The 23-kDa band corresponds with 'oxygen-evolving enhancer protein 2', an enzyme involved in the photosynthesis. The 50-kDa band corresponds with the heavy chain subunit of ribulose-1,5-biphosphate carboxylase/oxygenase (RuBisCo). This is a highly abundant protein in nature that catalyses a reaction that is rate-limiting for photosynthesis. Other possible allergens identified by Nayak *et al*. (Nayak et al., 2013) are glyceraldehyde-3-phosphate and adenosine triphosphate (ATP) synthase. Finally, the authors observed that ubiquitously distributed cross-reactive carbohydrate determinants (CCDs) might also be the cause of some IgE reactivity. Unlike the

European studies, in this American/Canadian study no ns-LTP sequences were identifiable and no IgE reactivity to this pan-allergen was demonstrable, even though IgE reactivity at approximately 10-kDa was observed in two patients. Moreover, in contrast to the European series, most of the Canadian patients apparently did not suffer from a cannabis-related cross-reactivity syndrome as is described below. Whether this indicates cannabis allergic patients to display geographically different sensitization profiles with distinct clinical outcomes remains to be established in larger collaborative studies. The most relevant cannabis allergens are displayed in table 1.

Clinical manifestations

The symptoms of an IgE-mediated cannabis allergy can vary considerably from mild to life-threatening reactions and frequently relate to the route of exposure. First, respiratory reactions like rhinoconjunctivitis, asthma and palpebral angioedema have been described. These reactions predominantly occur when cannabis is consumed by smoking or vaporizing (Swerts et al., 2014, Van Gasse, 2014, Ebo et al., 2013b). Respiratory symptoms may also arise from passive exposure to cannabis smoke by proxy or inhalation of *C. sativa* pollen (Ebo et al., 2013b, Stokes et al., 2000, Mayoral et al., 2008, Torre et al., 2007, Singh and Shahi, 2008, Prasad et al., 2009).

Handling of *C. sativa* plants may lead to contact urticaria (Williams et al., 2008, Majmudar et al., 2006) and contact dermatitis (Williams et al., 2008). Periorbital angioedema may occasionally be triggered by cannabis allergens that became airborne (Tessmer et al., 2012). Finally, anaphylaxis can result from ingestion of hempseed (Stadtmauer et al., 2003) and from drinking marihuana tea (Tessmer et al., 2012).

As already exemplified higher in the section “Cannabis allergens”, patients with IgE-mediated cannabis allergy can display distinct sensitization profiles such as sensitization to the ns-LTP of *C. sativa,* i.e. Can s 3. Non-specific lipid transfer PRP-14 proteins are pan-allergens ubiquitously present throughout the plant kingdom including fruits and vegetables (Egger et al., 2010). Consequently, sensitization to Can s 3 could be an explanation for the high variety of secondary plant-derived food allergies seen in European patients with a cannabis allergy. This, sometimes extensive, cross-reactivity between cannabis and plant-derived food has been described in (Ebo et al., 2013b) and was recently designated as the “cannabis-fruit/vegetable syndrome” by Van Gasse *et al* (Van Gasse, 2014). In our case-control series (Ebo et al., 2013b), 10/12 patients with a documented cannabis allergy were sensitized to different ns-LTPs including Pru p 3, the ns-LTP of peach (*Prunus persica*). The food allergies most commonly implicated in the cannabis-fruit/vegetable syndrome were allergies to peach, banana, apple, cherry, nuts, tomato and occasionally citrus fruits such as orange and grapefruit. Important to note is that these allergic reactions were more severe than the oral allergy syndrome (OAS) that is generally observed in food allergy related to sensitization to Bet v 1, the major birch pollen allergen (Ebo and Stevens, 2001). This could be explained by the fact that ns-LTPs resist to gastroduodenal proteolysis (Cavatorta et al., 2010, Wijesinha-Bettoni et al., 2010) and thermal processing (Scheurer et al., 2004, Sancho et al., 2005, Matejkova et al., 2009). However, it should also be kept in mind that in addition to plant food allergies, sensitization to Can s 3 might also explain cross-reactions to *Hevea* latex (Beezhold et al., 2003, Rihs et al., 2006, Quadri and Nasserullah, 2001, Faber et al., 2015b), alcoholic beverages such as beer and wine (Jegou et al., 2000, Asero et al., 2001) and tobacco (*Nicotinia tabaccum)* (Carnes et al., 2013, Faber et al., 2015a).

Figure 1 gives a non-exhaustive overview of this “cannabis-fruit/vegetable syndrome“.

As already exemplified in table 1, thaumatin-like proteins (TLP), belonging to the PRP-5 family, constitute another important group of components that might explain extensive cross-reactivity between cannabis and plant-derived food in European patients (Larramendi et al., 2013). These TLPs can be found in pollen and different foods such as NP24 from tomato (*Solanum lycopersicon*) (Sharma et al., 2011), Cup a 3 from cypress (*Cupressus arizonica*) (Breiteneder, 2004), Act d 2 kiwi fruit (*Actinidia deliciosa*) (Bublin et al., 2004) and Mal d 2 from apple (*Malus domestica*) (Hsieh et al., 1995).

Diagnosis

Although a thorough anamnesis is mandatory for correct diagnosis, it appears that history is frequently pieced together from inadequate description and recall by patients reluctant to admit or simply denying illicit drug abuse. History might also be misleading because of misinterpretation or misconception of symptoms related to active or passive exposure. For the time-being, sensitization and allergy to cannabis is almost exclusively studied or documented by prick-prick skin testing. Prick-prick skin tests use a broad variety of raw materials such as macerated *C. sativa* leaves, buds and flowers (Stadtmauer et al., 2003, Gamboa et al., 2007, de Larramendi et al., 2008, Tessmer et al., 2012, Nayak et al., 2013, Larramendi et al., 2013, Metz-Favre et al., 2011, Ebo et al., 2013b, Armentia et al., 2014). Needless to say that this approach is flawed by many issues and is virtually impossible to standardize, mainly because of unpredictable variations in composition and potential contaminations with other allergens of the raw material.

A second method that can be applied to document cannabis allergy is quantification of serum specific IgE (sIgE) antibodies towards industrial hemp, an assay that is readily available from Thermo Fisher Scientific (Uppsala, Sweden) but has not been thoroughly clinically

validated. In our series, a positive industrial hemp sIgE test was observed in all 12 cannabis allergic patients but unfortunately also in 3 out of 8 pollen allergic patients without cannabis allergy (Ebo et al., 2013b). Using a whole protein extract, Larramendi *et al* (Larramendi et al., 2013) found a positive sIgE result to a native cannabis extract in 21 out of 32 individuals who had their cannabis sensitization documented by a positive cannabis skin test.

During the last two decades significant advances in biochemistry and molecular biology enabled the characterization, cloning and recombinant synthesis of relevant allergenic components and epitope-emulating peptides enabling quantification of serum sIgE antibodies to these components or sequential epitopes; a method known as component resolved diagnosis (CRD). In contrast to traditional sIgE tests, CRD does not rely upon whole extract preparations but upon single native or recombinant components (e.g. proteins or peptide components) (Ebo et al., 2012, Valenta et al., 1999, De Knop et al., 2010). CRD involves unique marker components to study the genuine sensitization of patients towards a particular allergen and the presence of sIgE antibodies to cross-reactive components (e.g. profilins and CCD) that point to cross-reactivity. CRD not only allows to discriminate between genuine allergy and cross-reactivity, but also enables to establish individual predictive sensitization profiles which can be highly relevant in food allergy (Faber et al., 2014). In a study by Armentia *et al* (Armentia et al., 2014), sIgE antibodies against purified cannabis ns-LTP were demonstrable in over 95% of the patients with a primary cannabis allergy. Recently, Rihs *et al* (Rihs et al., 2014) succeeded to clone Can s 3 from *Cannabis sativa L ssp sativa cv Kompolti* and to study its IgE binding properties.

Other *in vitro* tests that have been employed to document sensitization to cannabis are histamine release tests (Herzinger et al., 2011) and basophil activation tests (BAT) (Ebo et al., 2013a). We found BAT with purified cannabis ns-LTP to be absolutely discriminative between

food allergic patients with and without cannabis allergy. In healthy control individuals no basophil responses to this purified cannabis ns-LTP were demonstrable (Ebo et al., 2013b).

Treatment

For the time being there is no cure for IgE-mediated cannabis allergy nor for the cannabis-fruit/vegetable syndrome. Therefore, strict avoidance measures are of utmost importance. These measures comprise an absolute stop of further abuse of the drug, and eventually also avoidance of exposures to allergens implicated in the individual cross-reactivity syndrome.

Natural history

The natural history of a cannabis allergy is currently unknown. Nevertheless, from an own study we observed that, although the patient stopped cannabis exposure, secondary food allergies can still evolve.

Conflict of Interest Statement

The authors report no conflict of interest.

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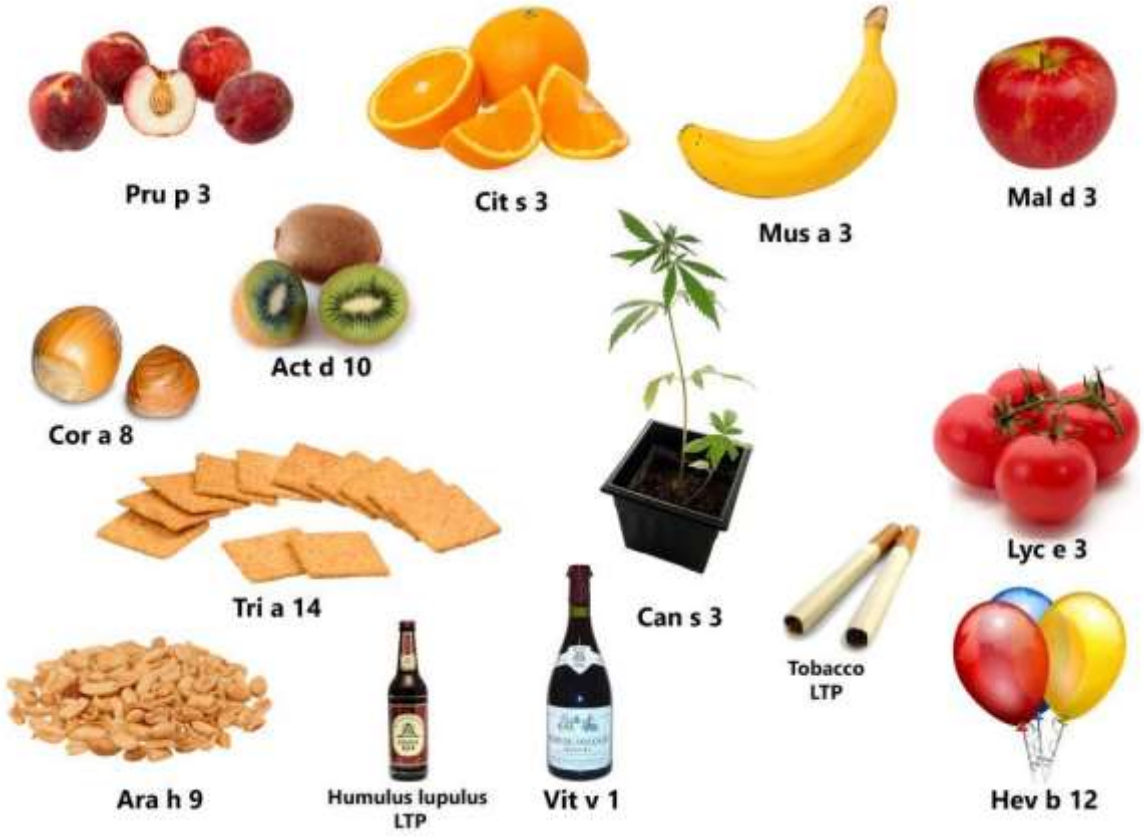
Table 1. Cannabis allergens				
Molecular weight (kDa)	Allergen	Function	Homologues (not exhaustive)	References
9	Can s 3	Ns-LTP (PRP-14)	Pru p 3, Mal d 3, Cor a 8, Hev b 12, Ara h 9, Tri a 14, Jug r 3	(Gamboa et al., 2007, de Larramendi et al., 2008, Larramendi et al., 2013, Metz-Favre et al., 2011, Ebo et al., 2013b, Armentia et al., 2014)
14	Profilin	Cytoskeleton	Bet v 2, Phl p 12	(Gamboa et al., 2007, de Larramendi et al., 2008)
23	Oxygen-evolving enhancer protein	Photosynthesis		(Nayak et al., 2013)
38	TLP (thaumatin-like)	PRP-5	Act d 2, Mal d 2, Mus a 4, Pru av 2, Cup a 3	(Larramendi et al., 2013)
50	Can s RuBisCo	Photosynthesis		(Nayak et al., 2013)

Figure 1. The cannabis-fruit/vegetable syndrome and other cross-allergies



Legend to Figure 1. Non-specific lipid transfer proteins (ns-LTPs) are ubiquitously present in the plant kingdom. Consequently, sensitization to Can s 3, the ns-LTP from Cannabis sativa, could lead to a broad variety of cross-reactions. Cross-reactive substances displayed in the figure: cherry (Prunus avium), tangerine (Citrus reticulata), orange (Citrus sinensis), peach (Prunus persica), apple (Malus domestica), tomato (Lycopersicom esculentum), hazelnut (Corylus avellana), walnut (Juglans regia), banana (Musa acuminate), wheat (Triticum aestivum), latex (Hevea brasiliensis), tobacco and alcoholic beverages such as wine (grapes: Vitis vinifera) and beer (common hop: Humulus lupulus).