Cannabis Allergy: What do We Know Anno 2015

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Received: 10 January 2015 / Accepted: 27 February 2015 / Published online: 16 July 2015
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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 or thaumatin-like proteins 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 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.

Keywords Allergy · Cannabis · Prevalence · Cannabis · Cross-reactivity · Diagnosis · IgE · CD63 · Basophil activation

Abbreviations

ATP	Adenosine triphosphate
BAT	Basophil activation test
Bet v	<i>Betula verrucosa</i> (birch)
Can s	<i>Cannabis sativa</i>
CCD	Cross-reactive carbohydrate determinants
CRD	Component resolved diagnosis
Cup a	<i>Cupressus arizonica</i> (cypress native to the southwest of north America)
PR	Pathogenesis-related protein
Pru p	<i>Prunus persica</i> (peach)
RuBisCo	Ribulose-1,5-biphosphate carboxylase/oxygenase
sIgE	Specific immunoglobulin E
THC	Tetrahydrocannabinol
TLP	Thaumat-like protein

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 contains 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

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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 (Herzinger et al. 2011; Spiwak et al. 2001; Williams et al. 2008), 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 that cannabis allergy will be an increasing problem in the future.

Routes of Exposure and Sensitization

With cannabis, various routes of exposure and sensitization can lead to primary cannabis allergy. First, people may become sensitized by inhalation of cannabis allergen through active smoking, and/or vaporizing the drug. Others may become sensitized by chewing, ingestion or intravenous use of the drug. Finally, cutaneous contact is another possible route of sensitization. This could be important in cannabis growers and police men seizing illegal cannabis plants. An alternative route of sensitization could be passive exposure by proxy when allergens become airborne or are transferred via contact. Furthermore, young children may be exposed to cannabis allergens, e.g. through smoking by parents and/or siblings (Ebo et al. 2013).

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. Pollen, once airborne, can be transported over extreme long distances (Freeman 1983; Mayoral et al. 2008; Prasad et al. 2009; Singh and Shahi 2008; Stokes et al. 2000; Torre et al. 2007). For example, in Nebraska, where industrial *C. sativa* is cultivated, *C. sativa* pollen accounts 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 less likely for abusers of cannabis, who grow their own plants, to become sensitized to marihuana through pollen exposure.

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 *C. sativa* (Can s) remains incompletely characterized. 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 (de Larramendi et al. 2008; Gamboa et al. 2007; Tanaka et al. 1998) and most likely corresponds to Can s 3, the ns-LTP of *C. sativa* (Gamboa et al. 2007) that belongs to the pathogenesis-related proteins (PR)-14 group (Van Loon 1999). In a study by 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 PR-5 family (Larramendi et al. 2013). Although in the study of Larramendi et al. (2013), no homology was found between the 14-kDa band and any known allergen, it was speculated that this band could be a profilin (de Larramendi et al. 2008).

In a study of Nayak et al. (2013), multiple IgE-binding proteins were observed although the 23- and 50-kDa seem to be the most prominent, even after deglycosylation, suggesting the IgE-binding epitopes not to reside in the carbohydrate moiety of the glycoprotein allergens. The 23-kDa band was identified as “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. (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 proteomics study, no IgE-binding sequences of the pan-allergen ns-LTP were observed, 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 (Ebo et al. 2013; Swerts et al. 2014; Van Gasse et al. 2014). Respiratory symptoms may also arise from passive exposure to cannabis smoke by proxy or inhalation of *C. sativa* pollen (Ebo et al. 2013; Mayoral et al. 2008; Prasad et al. 2009; Singh and Shahi 2008; Stokes et al. 2000; Torre et al. 2007).

Handling of *C. sativa* plants may lead to contact urticaria (Majmudar et al. 2006; Williams et al. 2008) 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 noted, 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 PR-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 by Ebo et al. (2013) and was recently designated as the “cannabis-fruit/vegetable syndrome” by Van Gasse et al. (2014). In our case-control series (Ebo et al. 2013), 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 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 (Matejkova et al. 2009; Sancho et al. 2005; Scheurer et al. 2004). However, it should also

Table 1 Cannabis allergens

Molecular weight (kDa)	Allergen	Function	Homologues (not exhaustive)	References
9	Can s 3	ns-LTP (PR-14)	Pru p 3, Mal d 3, Cor a 8, Hev b 12, Ara h 9, Tri a 14, Jug r 3	Armentia et al. (2014), Ebo et al. (2013), de Larramendi et al. (2008), Gamboa et al. (2007), Larramendi et al. (2013) and Metz-Favre et al. (2011)
14	Profilin (?)	Cytoskeleton	Bet v 2, Phl p 12	Gamboa et al. (2007) and de Larramendi et al. (2008)
23	Oxygen-evolving enhancer protein	Photosynthesis		Nayak et al. (2013)
38	TLP (thaumatin-like)	PR-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)

Except the study published by Larramendi et al. (2013) allergens described in the table have been suggested without deep investigation

Act d, *Actinidia deliciosa* (kiwi fruit); Ara h, *Arachis hypogaea* (peanut); Bet v, *Betula verrucosa* (birch); Can s, *Cannabis sativa*; Cor a, *Corylus avellana* (hazelnut); 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); Mal d, *Malus domestica* (apple); Mus a, *Musa acuminata* (banana); Ns-LTP, non-specific lipid transfer protein; Phl p, *Phleum pratense* (Timothy grass); Pru av, *Prunus avium* (cherry); Pru p, *Prunus persica* (peach); RuBisCo, ribulose-1,5-biphosphate carboxylase/oxygenase; Tri a, *Triticum aestivum* (wheat)

As described in Table 1, TLP, belonging to the PR-5 family, constitutes 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).

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. Presently, sensitization and allergy to cannabis are 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 (Armentia et al. 2014; de Larramendi et al. 2008; Ebo et al. 2013; Gamboa et al. 2007; Larramendi et al. 2013; Metz-Favre et al. 2011; Nayak et al. 2013; Stadtmauer et al. 2003; Tessmer et al. 2012). Needless to say, this approach is virtually impossible to standardize, mainly because of unpredictable variations in composition and potential contaminations with other allergens of the raw material.

(*Solanum Lycopersicum*), hazelnut (*Corylus avellana*), walnut (*Juglans regia*), banana (*Musa acuminata*), wheat (*Triticum aestivum*), latex (*Hevea brasiliensis*), tobacco (*Nicotiana tabacum*) and alcoholic beverages such as wine (grapes: *Vitis vinifera*) and beer (common hop: *Humulus lupulus*). Percentages represent sequence homology. ND no data (Boratyn et al. 2012)

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 commercially 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. 2013). Using a whole protein extract, 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. Herzinger et al. (2011) found positive sIgE results to marihuana and/or hashish in two patients with professional exposure to cannabis.

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; De Knop et al. 2010; Valenta et al. 1999). CRD involves unique marker components to study the 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 one to discriminate between genuine allergy and cross-reactivity, but also enables to establish individual sensitization profiles which can be highly relevant in food allergy (Faber et al. 2014). In a study by 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. (2014) succeeded to clone Can s 3 from *C. 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. 2013). 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. 2013).

Treatment

For the time being, there is neither cure for IgE-mediated cannabis allergy nor for the cannabis-fruit/vegetable syndrome. Therefore, strict avoidance measures are of utmost importance. These measures comprise a complete stop of further abuse of the drug, and 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, in a recent study, we observed that, although the patient stopped cannabis exposure, secondary food allergies can still evolve.

Acknowledgments The authors acknowledge the Agency for Innovation by Science and Technology (IWT-TBM: 140185). The authors also thank V. Sabato, a Clinical Researcher of the Research Foundation Flanders (FWO: 1700614N) and D. G. Ebo, a Senior Clinical Researcher of the FWO (1800614N).

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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