THE XPLORER

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INTERVIEW WITH ASSOC. PROF. WOLFGANG HEMMER, PHD

All about tropical fruit allergy

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THE ALLERGIC POTENTIAL OF TROPICAL FRUITS

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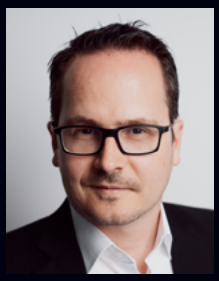


DEAR READERS,

At MADx, we have a clear goal: Become the global #1 allergy diagnostics provider. We aim to continuously improve molecular allergy diagnostics and make it accessible to as many people as possible. We are convinced that this goal can only be reached through constant research and innovation, changing diagnostics dogmas and consequent digitalisation.

Therefore, this year marks the beginning for several new projects and events for us. Exchanging ideas and engaging in discourse is what propels scientific research forward. We have always been proud to be part of an extensive scientific network.

With that in mind, this new e-magazine, THE XPLORER, was created. New editions will be released triannually, starting with this summery edition focusing on exotic fruits and their allergic potential.

In the second half of the year, we will launch the MADx Academy – a learning platform that will leave no questions about our products, technology, and the science behind it unanswered.

Furthermore, I am personally looking forward to welcome many of you to the first ever MADx Distributor Convention, which will take place on September 5th and 6th in Vienna this year.

As you can see, there is lots to be excited about when it comes to MADx in the upcoming months and years. We are happy to welcome you to this journey, and to share interesting and worthwhile content with you. So, without further ado, please enjoy the first issue of THE XPLORER.

Christian Harwanegg
CEO Macro Array Diagnostics

The allergic potential of tropical fruits

Interview with Assoc. Prof. Wolfgang Hemmer, PhD

From an allergologist perspective, which tropical fruits are the most important?

Prof. Hemmer: The importance of different tropical fruits depends on the one hand on how common sensitisation to such fruits is per se, and on the other hand on regional and individual dietary habits. In Central Europe, fruits that are eaten by many, such as banana, kiwi, mango, and fig are more likely to trigger allergic reactions than those that are rarely eaten, such as papaya and lychee.

How common are allergies to tropical fruits?

Prof. Hemmer: Overall, allergic reactions to tropical fruits are rare, with a few exceptions. Most forms of fruit intolerance occur secondarily as a result of cross-reactivity with certain inhalant allergens, so their frequency is closely related to that of the primary sensitiser. Fruit allergies that are based on cross-reactivity with pollen are the most frequent. In Central Europe, the cross-reactivity between birch pollen, kiwi, and fig should be mentioned first, where patients regularly report symptoms. Persimmons, jackfruit, and mulberries also contain a Bet v 1-type allergen. However, intolerance reactions are seen less frequently here due to limited consumption. Similarly, sensitisation to profilin is often associated with intolerance to certain tropical fruits, in practice particularly banana, melon, and mango. Fruit allergies occurring in the context of sensitisation to latex, Ficus benjamina or mugwort pollen, or in the context of an LTP syndrome, are rare in comparison, but usually clinically more severe.

What symptoms can be expected from an allergy to tropical fruits? How high do you estimate the proportion of severe, systemic reactions?

Prof. Hemmer: The symptoms of fruit allergies associated with birch pollen or profilin allergy are usually mild and limited to an oral allergy syndrome. However, this can sometimes be severe and accompanied by significant respiratory distress. In latex, ficus and mugwort pollen-associated fruit allergies, on the other hand, systemic symptoms (urticaria, angioedema, vomiting, hypotension) regularly occur, as do genuine allergies to kiwi. Systemic reactions are also possible in fruit allergies in the context of an LTP syndrome. However, severe life-threatening anaphylaxis is rare and often associated with exacerbating cofactors.

What is the diagnostic procedure for suspected allergy to tropical fruits?

Prof. Hemmer: If, after a thorough history, a specific allergy to a tropical fruit seems possible, the suspected diagnosis can be supported by skin and/or blood tests. In the absence of suitable test extracts, skin testing is essentially based on the prick-to-prick method, which is

usually very sensitive and specific, and has the advantage of detecting sensitisations that cannot be satisfactorily detected with the currently available blood tests. In in-vitro testing, multiplex methods using allergen chips have the great advantage of simultaneously visualising the numerous possible cross-links in allergies to tropical fruits. In the case of single tests, sufficient knowledge about probable or possible connections is required to confirm or exclude the molecular background of a fruit allergy by selecting suitable marker allergens.

What are the therapeutic approaches for a confirmed allergy to tropical fruits?

Prof. Hemmer: As with most other food allergies, avoidance of these fruits is the primary therapeutic measure. This is usually easy to implement in practice, and repeated reactions after accidental consumption are rare. In case of systemic pre-reactions, the provision of emergency medication including adrenaline pens may be necessary. Specific desensitisation strategies in the sense of oral tolerance induction, as is frequently practised for egg, milk, and peanut, appear to be of little use considering the ease of avoidance. In the case of birch pollen-associated fruit allergies, specific immunotherapy with birch pollen can lead to an attenuation of the associated food intolerances. The extent to which this particularly affects intolerance to kiwi, fig or other birch pollen-associated tropical fruits has not been investigated.

What in-vitro diagnostic options are available and where do you see room for improvement?

Prof. Hemmer: In principle, testing with total extracts is available for most tropical fruits as a first step. This is usually only useful to a limited extent because extracts do not provide information about the responsible allergens, about the possible cross-links resulting from them and about the risk of anaphylaxis. It is also questionable whether extracts always contain all relevant allergens and can reliably detect sensitisation. In the meantime, numerous marker allergens from different allergen families are available, through whose testing the fruit allergy and its origin can be characterised more closely. Some forms of fruit allergy, however, are only rather unsatisfactorily covered at the molecular level. This concerns, for example, the mugwort pollen-associated fruit allergies to mango and lychee, where the responsible allergens remain unclear. Another case is the Ficus-associated fruit allergies, where besides fig, kiwi, papaya, pineapple, and banana also play a role (Ficus-fruit-syndrome).

> "Fruit allergies are most frequently based on cross-reactivities with pollen."

Genuine allergy vs. cross-reactions: What role do CCDs and cross-reactive allergen families play?

Prof. Hemmer: Most allergies to tropical fruits are not genuine, but occur as a result of cross-reactions with inhalant allergens, such as birch pollen, mugwort pollen, profilin, latex, ficus or papain. Even in LTP syndrome, where tropical fruits are of limited overall importance, the primary sensitisation is usually not directed against the tropical fruit. Probably only a few fruit allergies can be classified as genuine, e.g., some forms of kiwi and banana allergy. Cross-reactive allergen families and panallergens therefore play a major role overall. It is therefore even more important to use all available marker allergens in the serological clarification of fruit allergies to be able to delineate the origin of the sensitisation and its potential relevance as precisely as possible. Extracts should only be used when suitable components are not available or as a supplement because, apart from their uncertain sensitivity, they are not very specific and too often give misleading "false-positive" results due to CCD interference.

Which allergen families are of particular importance here?

Prof. Hemmer: The list of relevant allergen families is long: PR-10 proteins in birch pollen-associated tropical fruits (kiwi, fig, persimmon, jackfruit, mulberry), additionally also isoflavone reductases as a birch pollen mini-allergen (Bet v 6) with cross-reactions to food (e.g. banana), profilin as a panallergen (important in e.g. banana, mango, mango, mulberry). Hevein or class 1 chitinases with hevein domains (Hev b 6/11) and b-1,3-glucanases (Hev b 2) in latex fruit syndrome (kiwi, banana, fig, avocado, passion fruit, etc.), and finally cysteine proteases (thiol proteases) in ficus-associated fruit allergies. Also important are the nsLipid transfer proteins as further panallergens, where with the kiwi Act d 10 an LTP from a tropical fruit is also testable. The significance of thaumatin-like proteins (TLPs), which could play a role in reactions to kiwi (Act d 2) and banana, among others, is controversially discussed. It is also unclear which allergens are responsible for the intolerance of mango and lychee in some mugwort allergic patients. There is some evidence for defensins in these fruits, i.e., homologues of the main mugwort allergen Art v 1. Recently, peroxiredoxin and inositol phosphate synthase have also been discussed as novel mango allergens.

How do you view the role of currently available molecular allergy diagnostics in this field?

Prof. Hemmer: The currently available allergens already cover a large part of the known fruit allergies, but by no means completely. Especially in the case of fruits with a high potential for systemic reactions, there are considerable gaps, particularly in the case of ficus and mugwort pollen-associated food allergies, where one is essentially dependent on skin testing or IgE testing with total extracts. However, according to our own observations, total extracts are not very sensitive, especially in the case of mugwort-associated allergies.

What would you like to see from test manufacturers (molecular allergens or extracts)?

Prof. Hemmer: A very helpful component would be the cysteine protease ficin from Ficus benjamina or from the fig (Fig c 2), which would not only be important in differentiating between a (harmless) birch pollen-associated fig allergy and a (potentially dangerous) ficus-associated fig allergy, but also represents a clinically relevant inhaled indoor allergen. The cysteine proteases currently available on the market, papain (papaya) and bromelain (Ana c 2, pineapple), are natural purified proteins with CCD reactivity. For the reliable identification of papaya and pineapple allergies, recombinant allergens would be advantageous. Regarding mugwort pollen-associated mango and lychee allergies, basic research is required to identify the responsible allergens. In the field of LTP allergies, further representatives from tropical fruits would be helpful, e.g., from banana and pomegranate.

How well researched is this topic?

Prof. Hemmer: Many studies on this topic and especially on the identification of the responsible allergens date back quite some time. More recently, the topic has been addressed repeatedly, but overall, many details about the relevance of the different allergen groups remain incompletely clarified, and some allergens are still not identified with certainty.

ABOUT

ASSOC. PROF. WOLFGANG HEMMER, PHD

studied biology at the University of Vienna (AT) and obtained his PhD at the Institute of Zoology. Since 1993, he has been working in the scientific department at the FAZ focusing on inhalative-, secondary food- and insect venom- allergy. In 2004, he habilitated at the Medical University of Vienna in allergology/immunology.

> "The primary therapeutic measure is avoidance of the fruit allergen."

Banana allergy

True allergy, latex-fruit syndrome, and pollen-food syndrome

Banana (Musa acuminata) is a common fruit integrated in the human diet. Due to the high nutritional content, bananas may be the best quick fruit snack for sustained energy. While they are a good natural source of sugar, they are also rich in fibre, potassium, vitamin B6, vitamin C and various antioxidants and phytonutrients – all helpful nutrients that make the body feel energised.

Because of their soft texture, bananas are usually introduced early in the infant diet. Based on its extensive consumption and early introduction, bananas should be considered as a putative relevant food allergen source that may lead to an increase of symptomatic cases in the infant population.

Allergy to banana affects around 0.04%-1.2% of the general population across the world. (El-Sayed) However, an increasing trend on the number of cases on hypersensitivity reactions to banana in infants as well as in adults are being reported to date. Ingestion of fresh, uncooked banana fruit is the main cause of allergy as most banana allergens are sensitive to heat.

CLINICAL MANIFESTATIONS

Clinical manifestations of banana allergy range from mild, local symptoms referred to as oral allergy syndrome (OAS) to severe, systemic, life-threatening anaphylaxis. (Nikolic) Various phenotypes of banana allergy have been identified, among them true banana food allergy, latex-fruit syndrome and it can also be associated with pollen allergy. Extensive cross-reactivity of banana with latex, pollens (olive, birch, palm, ragweed, and hazelnut), and fruits (melons, peach, kiwi, avocado, and pineapple) has been observed.

TRUE BANANA ALLERGY

True banana allergy is neither led back to pollen nor latex sensitisation but can lead to severe anaphylactic reactions. (Savonius) When banana is the primary sensitiser, the patient is

suffering from true banana allergy. Banana food allergy is rare, however affected patients have an increased risk to suffer from severe anaphylactic reactions.

LATEX-FRUIT SYNDROME

Latex-fruit syndrome occurs in patients who are allergic to natural rubber latex, due to similarities between latex and banana proteins. Banana is also highly associated with sensitisation to other foods such as avocado, kiwi and chestnut, called latex-fruit syndrome.

It has been observed that 20-50% of patients allergic to natural rubber latex have experienced symptoms after eating banana, due to cross-reacting allergens. The latex-fruit syndrome is caused by cross-reactivity between Mus a 2 and Hev b 2 from latex.

POLLEN-FOOD-SYNDROME

In patients sensitised to certain tree pollens (e.g., birch, alder, hazel), cross-reacting proteins may be involved in pollen-associated banana allergy. Patients may develop mild symptoms after banana consumption.

BANANA ALLERGENS

So far, six allergenic proteins from Musa acuminata have been listed officially. (WHO) Mus a 1 (Profilin), Mus a 2 (Chitinase), Mus a 3 (Lipid-transfer protein), Mus a 4 (Thaumatin-like protein), Mus a 5 (b-1,3-glucanase) and Mus a 6 (Ascorbate Peroxidase).

However, most cases of banana allergy are caused by profilin sensitisations. The cross-reacting IgE antibodies specific for the major birch pollen allergen Bet v 2 and latex Hev b 8, have been shown to cross-react with homologous proteins from banana (Mus a 1) resulting in oral allergy syndrome. Mus a 1 is a profilin, revealing IgE-reactivity in 44% of suspected banana allergic patients. (Reindl)

Three proteins – Mus a 2, Mus a 4 and Mus a 5 have been characterised as major banana allergens. (Palacin) Importantly, Mus a 5 can be classified as a marker for banana allergy in molecular allergy diagnosis, especially in banana allergic patients with negative test results for banana extract.

Allergen	Biochemical name	Specific IgE-reactivity	Allergenicity	Reference
Mus a 1	Profilin	rMus a 1: 44%	• Highly cross-reacting with birch (Bet v 2) and latex (Hev b 8) profilin • Sensitive to heat and digestion	Reindl
Mus a 2	Class I chitinase	50%	Major allergen	Sanchez-Monge
Mus a 3	Non-specific lipid transfer protein (nsLTP)	20%	PR-14 protein family	Palacin
Mus a 4	Thaumatin-like protein (TLP)	72%	• Major allergen in pediatric population • 50% had positive skin prick test results	Palacin
Mus a 5	Beta-1,3-glucanase	74-84%	• Major banana allergen • SPT positive in 20%	Palacin Aleksic
Mus a 6	Ascorbate peroxidase	nMus a 6: 91% rMus a 6: 64%	Most recent identified allergen	WHO

CASE 1 (O'Keefe)

A 4-month-old Hispanic baby boy suffering from eczema was taken to the emergency room with vomiting, urticaria and cyanosis following first exposure to a banana. He improved with administration of intramuscular epinephrine. Skin prick tests showed positive results for both fresh banana and banana extract. This case shows that very severe allergic reactions can be caused by bananas.

CASE 2 (Hauswirth)

A 7-month-old boy suffered from atopic dermatitis and angioedema/erythema during his first introduction to cow's milk formula. He was exclusively breast-fed until this point. At 5 to 6 months of age, he was introduced to solid foods. Approximately 2 hours after an isolated feeding of crushed banana, he awoke from a nap with generalised urticaria, vomiting, and respiratory symptoms, including wheezing. He was immediately taken to the emergency room for appropriate treatment. He had been fed banana on one previous occasion, several weeks before this ingestion, without symptoms. He had no history of reaction to substances that cross-react with banana, including latex. Initial SPT result with a commercial milk extract was positive, the SPT result with commercial banana extract was negative. Because of his convincing history, a prick-prick test with fresh banana was performed, resulting in a 20 mm × 20 mm wheal. Further testing included a CAP-FEIA (Pharmacia, Uppsala, Sweden) to banana, with a level of 4.70 kU/L.
This patient's case illustrates one of the pitfalls in the evaluation of fruit allergy. Commercial extracts for food and fruit testing are not standardised. (Akkerdaas) This case demonstrates that fresh fruit-induced anaphylaxis may be missed if commercial extracts alone are relied on for diagnosis in the setting of a suggestive clinical history.

DIAGNOSIS

For definite diagnosis of banana allergy, a combination of skin prick test, determination of allergen-specific serum IgE antibodies and food challenge test should be applied.
Since species-specific banana allergens as well as cross-reactive allergens play a role in banana allergy, component-resolved diagnostics including all six banana allergens (Mus a 1 – Mus a 6) are useful for clinical classification and diagnosis.
As food allergy becomes more prevalent, foods once believed not to cause systemic symptoms will increasingly require more in-depth clinical evaluation.

Coconut allergy

True food allergy and contact dermatitis

IT IS A FRUIT, NOT A NUT

Coconut is the stone fruit of the coconut palm (Cocos nucifera) which has been grown in tropical regions for more than 4,500 years. It is a high-fat fruit that has a wide range of health benefits. These include providing the human body with disease-fighting antioxidants, promoting blood sugar regulation, and reducing certain risk factors for heart disease.
Given the increasing use of commercially available coconut products, it is important to be aware of the allergenic potential of coconut. Coconut allergy is very rare, however allergic reactions tend to be systemic.

NUTRITIONAL ASPECTS

Coconut has increasingly become part of the human diet and is a popular alternative beverage for children with cow's milk allergy but also for people following a vegan diet. Its popularity has increased due to its pleasant flavour, culinary uses, and potential health benefits. Coconut is used for its water, milk, oil, and tasty meat. The pulp can be eaten raw or used in baking as coconut flakes. The oil and milk derived from the coconut are commonly used in cooking and frying.

SKIN CARE

Coconut has been popularised in the cosmetics and skincare industry. It is remarkable that coconut is the most common food allergen present in commercially available skincare products. Natural moisturisers are often used for babies, particularly children with atopic dermatitis (Silverberg) or very dry skin. Approximately 75% of shampoos and body soaps contain coconut. (Newhall)

Thus, sensitisation to coconut allergens via the skin is often underestimated. In infants, applying coconut to inflamed skin and not engaging in oral consumption is a concerning set-up for percutaneous sensitisation and ultimately food allergy, not oral tolerance. (Du Toit)

Coconut-derived products (such as coconut diethanolamide, cocamide sulphate, cocamide DEA, CDEA) present in cosmetics including hair shampoos, moisturisers, soaps, cleansers, and hand washing liquids can cause contact dermatitis. As with any contact dermatitis, an itchy blistering rash may arise a day or two after contact with the allergen and take several days to resolve. If contact dermatitis to coconut products is suspected, then patch testing is an appropriate method for diagnosis.

> "Approximately 75% of shampoos and body soaps contain coconut."

CLINICAL MANIFESTATIONS

Coconut is associated with a wide range of allergic reactions in children. Topical, breastfeeding, and ingestion exposures are associated with symptoms. Reactions can present as atopic dermatitis flare, urticaria, mild oral symptoms, and mild/moderate anaphylaxis. No reactions by means of skin contact or breastfeeding resulted in anaphylaxis.

Coconut allergy is becoming a more common concern among parents of children with food allergy. Food allergic patients (especially tree nut allergic patients are often encouraged to avoid coconuts) are frequently uncertain whether they can safely consume coconut products. In a study of children with allergy to tree nuts, coconut sensitisation was reported to be 30%. (Polk) Interestingly, a higher risk for allergy vs. sensitisation was observed in Asian and African American patients, at 2-fold and 1.5-fold respectively. This might reflect an increased coconut consumption or topical application. For peanut food allergy, it has already been demonstrated that topical exposure to food allergens in associated with an increased risk of food allergy. (Lack) For example, soy, coconut, and walnut co-sensitisation is common due to seed storage proteins. (Teuber) This suggests that sIgE testing to these foods might reveal co-sensitisation, but not necessarily clinical reactivity. Of the tree nuts, macadamia nut had a strong correlation with coconut, possibly due to homology between coconut and macadamia seed storage proteins. (Kruse, Polk, Geiselhart)

CASE STUDY 1 (Anagnostou)

A very interesting case of coconut allergy was reported in a child that was previously tolerant to coconut, regularly exposed via the skin and gastrointestinal route. The child has been exposed to pure coconut oil since the they were two weeks of age and subsequently also via the oral route. The patient was eating coconut regularly without any symptoms. Tolerance was maintained until the age of six. After that the patient experienced generalised urticaria after coconut oil application on the skin. Additionally, the child complained several times about a 'scratchy throat', suffered from severe abdominal pain, vomiting and diarrhea after eating coconut ice cream or coconut-containing meals.

CASE STUDY 2 (Tella)

A 3-year-old boy suffered from abdominal pain, vomiting and oral allergy syndrome immediately after oral contact with coconut sweets. One year later, he ate a piece of fresh coconut and the same symptoms occurred. Skin prick tests to common foods were negative, however a weak wheal to almond but a strong wheal to coconut were observed. Serum-specific IgEs to coconut were elevated (RAST class 3). In that report, IgE binding proteins of 55, 36.5, and 35 kDa were observed on coconut protein immunoblots and these bands were immunologically cross-reactive with seed storage proteins from walnut, almond, and peanut. Furthermore, studies of the major albumin and globulin proteins in coconut endosperm have indicated immunologic cross-reactivity with the soy globulins conglycinin and glycinin (De Mason). Moreover, a coconut 35 kDa protein is known to share similar physical and biochemical characteristics with other globulins of the legumin group, including soybean glycinin, peas legumin and peanut arachin. (Carr) In conclusion, in the present case, the young child and the lack of other food and pollen allergies suggest coconut hypersensitivity to be a true primary sensitising agent and not a cross-reactive one.

COCONUT ALLERGENS

Few allergens have previously been identified as coconut allergens: Coc n 1 (7S Vicilin-like globulin) (Saha, Saha), Coc n 2 (7S Vicilin-like globulin) (Benito), Coc n 4 (11S globulin) and Coc n 5 (Profilin). Previous studies revealed cross-reactivity between coconut and tree nuts (Polk), buckwheat (Cifuentes) and lentils (Manso). Although sensitisation to most tree nuts appears to correlate with coconut, this is largely explained by sensitisation to almond and macadamia. Coconut allergy seems to be rarer than buckwheat allergy but potentially more severe. Results of immunological studies provided evidence that both allergens, 7S and 11S globulin, were involved in this cross-reactivity.

DIAGNOSIS

Coconut allergy is as a new cause of hidden food allergy that should be kept in mind when evaluating allergic patients.
Upon evaluating the clinical history of a patient, extracts of coconut are available for blood allergy tests as well as skin prick testing. Coconut sensitisation, determined by skin prick and sIgE testing is associated with an approximately 50% and 60% risk for clinical reactivity, respectively. SPT and sIgE testing can be used to help guide clinicians in determining the probability of reaction. However, further work is needed to improve the clinical use of coconut allergy diagnostics. In order to offer precise allergy tests based on molecular components, further research on individual coconut allergens is needed.

Jackfruit allergy

After primary sensitisation to birch and latex

The jackfruit is the world's largest edible fruit, sometimes exceeding 55 kg of weight and a yield of up to 500 fruits per tree and year. Its name originates from the Malayalam word "chakka", meaning "round", and was converted via the Portuguese word "jaca" into the commonly known name "jackfruit". Taxonomically, the species Artocarpus heterophyllus Lam. belongs to the family Moraceae (order Rosales, class Magnoliopsida) that accommodates other prominent members, such as mulberry, fig, or breadfruit. Originating from southern India, Sri Lanka, Malaysia, Indonesia and the Philippines, the jackfruit tree was spread throughout Southeast Asia, South America, the Caribbean, Australia, and Africa. Due to its widely appreciated flavour, consumption of jackfruit is very common in those areas, mostly as fresh, ripe fruit but the unripe fruit can also be consumed cooked and used for savoury dishes, as substitute for meat. Jackfruit contains considerable amounts of latex which becomes immediately apparent when cutting the fruit, covering both hands and knives with a sticky sap.

AS AN ALLERGEN SOURCE

Data on the role of jackfruit as an allergen source are rather scarce – except for one larger study, mostly confined to case reports. Until now, only two allergen molecules, Art h 1 (Bet v 1-like) and Art v 4 (profilin) have been described (www.allergome.org) but not officially registered in the IUIS-database. Essentially, in most cases clinical and IgE-reactivity were suggested to be attributable to cross-sensitisation either with birch pollen or latex, but hardly due to primary sensitisation to jackfruit. This notion was corroborated by IgE-inhibition studies, as exemplified below.

SYSTEMIC REACTIONS

In a study by Bolhaar et al. from 2004, two patients with known allergy to birch pollen

were reported to have experienced severe systemic reactions to jackfruit upon the first time of consumption. Allergy to jackfruit subsequently was confirmed by positive prick-to-prick test and DBPCFC. In addition, five subjects with birch pollen allergy, suffering from OAS to apple, were enrolled who previously never had contact to jackfruit but, during oral challenge, also experienced strong reactions. By immunoblot it was revealed that all patients had IgE specifically binding to a 17 kDa band which could be completely inhibited by preincubation of the sera with Bet v 1 or birch pollen extract. Hence, the authors concluded that in those patients, allergic reactions to jackfruit occurred after primary sensitisation to birch pollen and that the presence of OAS indicated a higher propensity of a severe reaction. This notion was supported by a similar case published as conference contribution and by a larger study enrolling 85 patients exclusively allergic to birch pollen of which 91% showed reactivity to jackfruit and, in addition, to many other fruits of the Moraceae family (fig, mulberry, maclura) in prick-to-prick testing. Again, complete inhibition of IgE-binding to a 17 kDa protein in all fruit extracts was achieved by pre-incubation of sera with Bet v 1 or birch extract, confirming cross-reactivity due to IgE specific to Bet v 1-homologues. However, since most study participants had never been exposed to jackfruit so far, the clinical relevance of this cross-sensitisation could not be assessed. Two individuals who actually had consumed fresh jackfruit reported either mild OAS or more severe symptoms, including respiratory distress, respectively.

LATEX-FRUIT-SYNDROME

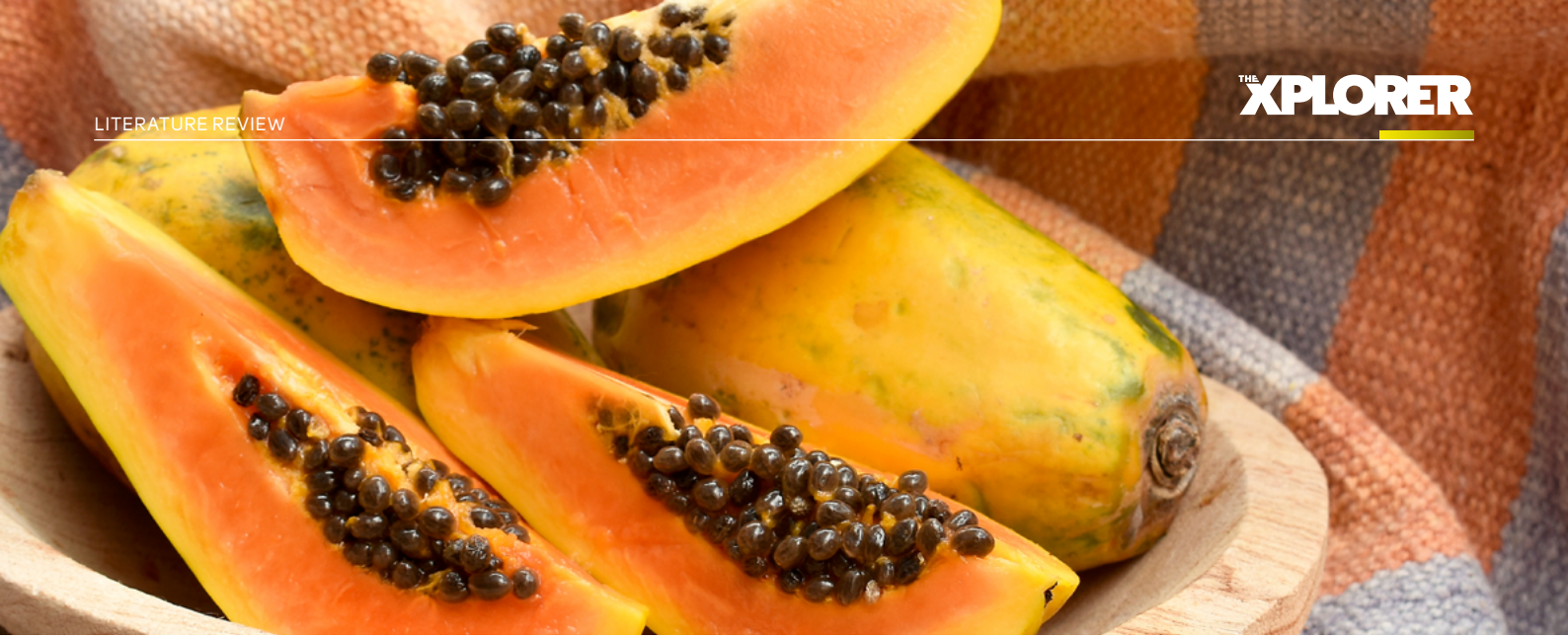
By contrast, allergic reactions after ingestion of dried jackfruit were primarily seen in patients with concomitant sensitisation to latex. In those two case reports, both patients who had been previously diagnosed with allergy to latex, experienced severe anaphylactic reactions after ingestion of dried jackfruit. However, in those reports, allergic sensitisation was neither analysed at a molecular level nor by IgE-inhibition experiments. It therefore remains to be determined if in such cases, allergic reaction to jackfruit is, as implied by the results, truly a clinical manifestation of the latex-fruit-syndrome.

UNCLEAR CASE STUDY

Finally, in one of the first papers on allergy to jackfruit dating back 25 years, OAS after jackfruit consumption was reported in a patient originating from the Philippines who had been living in Switzerland for several years. Notably, allergic reactions to jackfruit have only appeared after the patient had developed clinical symptoms of pollinosis to trees (including birch), grass and weeds. However, as inhibition experiments using Bet v 1 and Bet v 2 as inhibitors did not reduce IgE-binding to jackfruit extract, the precise nature of the observed co-occurrence of allergic reactions remained unclear.

SUMMARY

- In those cases of jackfruit allergy reported so far, clinical reactivity to jackfruit was suggested to be a secondary reaction after primary sensitisation to birch pollen or latex.
- Severe anaphylactic reactions to jackfruit are rare and were reported only in association with latex or birch pollen allergy. OAS to PR-10 food allergens probably indicates an elevated risk of more severe symptoms.



Papaya allergy

Occupational allergies and latex-fruit-syndrome

The word "papaya" is thought to be derived from Arawak language, a group of indigenous people in South America and the Caribbean, most likely being the original word for the fruit itself. The Aztecs had a different, more tongue-twisting name for the fruit: "chichihualtzapotl", meaning "nurse fruit" and presumably referring to the notion that the fruit had a fostering effect on fertility. The other part of the complete taxonomic designation, "Carica", is of Greek origin and means "fig", probably due to the fig-like shape of the leaves of the papaya plant.

CULTIVATION AND USE

Taxonomically, the species Carica papaya L. belongs to the family Caricaceae of the order Brassicales and the class Magnoliopsida (source: www.itis.gov). Originating from the South of Mexico and Central America, it has been spread in nearly all tropical regions and is cultivated and harvested from India and Oceania, as well as Central Africa to South America. Even though it resembles a tree, the papaya plant is classified as an herbaceous perennial since it is lacking a woody trunk. The fruits (botanically classified as a berry) can become quite big, i.e., up to 90 cm in size and 10 kg of weight, and possess a melon-like shape. Therefore, there is another alternative, popular designation for the papaya: "tree melon". Most commonly, the papaya is consumed as a ripe, fresh fruit, but also the unripe green fruit can be used, yet needs to be cooked because of its latex content. In some regions, the leaves of the plant are used for savoury dishes as well. Papain, a cysteine-protease found in the latex of the fruit is a widely used additive, e.g., as a meat tenderiser or in the biopharmaceutical industry.

2 REGISTERED ALLERGENS

So far, two allergens from Carica papaya L. have been registered in the IUIS-database (www.allergen.org) which were found both in the pollen of the plant and the fruit itself: Cari p 1, an endo-polygalacturonase, and Cari p 2 (chymopapain).The latter is a heat-labile cysteine-protease with a molecular weight of 28 kDa, which was previously used for the treatment of herniated vertebral discs by chemonucleolysis, a treatment which has been abandoned for the significant risk of allergic sensitisation. A study by Bhowmik et al. describes that of 14 patients with "outdoor respiratory

symptoms" and a positive skin reaction to papaya extract, 11 (78%) showed IgE-reactivity with Cari p 2, and eight exhibited additional symptoms of food allergy after the consumption of papaya. Cross-inhibition studies with blotted extracts from pineapple, kiwi, soybean, papaya pollen, and papaya fruit showed that preincubation with Cari p 2 inhibited binding to corresponding Cys-proteases from kiwi and pineapple, in addition to auto-inhibition with papaya fruit and pollen.

> "Papaya allergy initially was described as occupational disease in employees of the food industry."

LATEX-FRUIT-SYNDROME

Other allergen molecules from Carica papaya, as reviewed by Rojas-Mandujano and enlisted at www.allergome.org, are Cari p papain (previously designated Car p 1 and Car p 3), caricain, glycylendopeptidase (all three allergens are cysteine endoproteinases) and Cari p chitinase (class I chitinase). Apart from chitinase, which is found both in the fruit and the pollen of the papaya plant, the former three were isolated only from the fruit. Cross-reactivity between latex and papaya, as manifestation of the latex-fruit-syndrome (LFS), is suspected to be attributable to shared epitopes of class I chitinases from papaya and from rubber latex (Hev b 6 and 11), respectively. Notably, severe allergic reactions were more frequently observed in subjects suffering from LFS compared to patients monosensitised to rubber latex. This was demonstrated by a study enrolling 11 patients with diagnosed latex allergy and a history of clinical reactivity to papaya (designated by the authors as "latex-papaya-syndrome"). Among all 11 subjects, seven exhibited an anaphylactic reaction during skin testing with latex extract, representing an unusually high proportion. To avoid any further severe systemic reactions, prick-to-prick testing with fresh papaya was omitted, particularly because some patients had reported severe reactions upon previous exposure to the fruit.

PAPAIN AS AN ALLERGEN

Apart from class I chitinase, papain is another frequent inducer of clinically relevant sensitisation to papaya. Based on studies investigating allergic sensitisations to papain after the late 1970s, papaya allergy initially was described as occupational disease in employees of the food-, pharmaceutical, beer- and cosmetics industry. In several case reports, mostly respiratory but also more severe systemic reactions were described in industrial workers who were repeatedly exposed to papain powder. In those papers, IgE-sensitisation was confirmed by RAST and SPT. In Baur et al., bronchial provocation was additionally performed, demonstrating that papain exhibits a high capacity to trigger allergic reactions even at low doses. Apart from occupationally exposed subjects, sensitisation to papain was rarely observed as revealed by routine SPT-screening of 330 subjects, although papain is contained in many domestic and medicinal products. However, apart from immunologically mediated alterations in response to incorporation of papain via the respiratory route, the latter can also result in direct damage of lung tissue, i.e., lung emphysema, due to its enzymatic activity.

STUDIES ON CROSS-REACTIVITY

The existence of different allergen molecules present in pollen of the papaya plant compared to the fruit was investigated by

Blanco et al. In that study, six subjects with seasonal respiratory symptoms (rhinitis and/or asthma) suggestive of being related to papaya pollen exposure, but clinical tolerance to or no consumption of papaya fruit were enrolled. While all subjects had IgE to extracts from papaya pollen, fruit and to papain and were positive in conjunctival provocation performed using papaya pollen extract, only three also showed reactivity with papaya fruit extract and/or papain in skin testing. Notably, in neither patient IgE-reactivity to papaya was associated with clinical symptoms. RAST inhibition experiments with papaya pollen extract on the solid phase and extracts from pollen, fruit, or papain, respectively, as inhibitors showed complete autoinhibition and almost complete inhibition using papain, but only 72% inhibition using the fruit extract. However, the nature of this strong cross-reactivity between pollen and fruit – probably mediated by profilins – remained unanswered, as was the question to what extent the apparent inhibitory activity of papain was attributable to its enzymatic activity, interfering with the experimental setup.

FICUS-FRUIT-SYNDROME

Regarding other potential cross-reactivities, no association with birch pollen, i.e., with PR-10 allergens, was found. However, a considerable proportion (24%) of subjects with allergy to Ficus benjamina, i.e., even more than in Latex allergic subjects (9%) proved positive to papaya fruit in prick-to-prick testing. This paper confirmed previous results having convincingly suggested the existence of a "Ficus-fruit-syndrome". In the latter study, a similar proportion (22%) of patients with allergy to Ficus benjamina had reacted in SPT with papaya extract. In those trials, the clinical relevance of this unexpectedly high rate of cross-sensitisation probably was underrated due to the infrequent consumption of papaya in the study population. However, in those papers the authors could show that cross-reactivity between different, distinct fruits such as fig, papaya, kiwi, and banana in many cases is likely due to sensitisation to structurally related proteases, including papain.

SUMMARY

- Both pollen and fruit of the papaya plant can induce allergy.
- Most papaya allergens are cysteine-proteases, including papain.
- Papain is a relevant occupational allergen in the biopharmaceutical and food industry. Papain-sensitised subjects can experience cross-reactivity with other fruits (kiwi, banana, fig).
- Papaya class I chitinase can mediate cross-reactivity with latex (latex-fruit-syndrome).

A global perspective on molecular allergy diagnostics

With Dr. Christian Harwanegg, CEO of MADx

MADx focuses on molecular allergy diagnostics and is already represented in more than 60 countries with the ALEX. But what is the global perspective on allergy diagnostics?

Christian Harwanegg (CH): Manufacturers of allergy diagnostics divide the world into different classes: first world, second world, third world. In the first world - for example, the core countries of Europe, the USA and Japan - allergy diagnostics are already widespread.

In the second world, in the so-called emerging countries, the structures are much more dynamic due to rising living conditions, better nutrition, and more health awareness. An example is East Germany after the fall of the Berlin Wall, where there was a big increase in allergies due to the newly achieved prosperity.

When we talk about third world countries, you have to remember that people's immune systems are constantly bombarded with germs, parasitic diseases, malaria, and HIV. Allergies do exist there, but they are not a big issue because people's immune systems are busy with other problems.

In a way, allergy is a "first world plus" and hygiene problem. In this context, it will also be interesting to see what will happen after the COVID-19 pandemic - after years of wearing masks and constantly disinfecting our hands, and children having little contact with other children, relatives, or dirt.

How are allergies currently diagnosed, are there different preferences on different continents?

CH: There are different schools of thought. In Europe, molecular diagnostics is the most advanced. Austria is and was also strongly represented in research here. The Medical University of Vienna was a leading centre in the invention and establishment of molecular allergy diagnostics in the 1980s.

In many parts of the world, in-vivo provocation (e.g., administration of food, pricking the skin, etc.) is still very dominant. According to first-world prevalence data, we can assume that 30% of people are sensitised, but only a fraction of them are actually tested for allergies. Many allergy sufferers are never tested during their lifetime. When testing is done, it is usually in-vivo. Skin tests, patch tests and provocation tests are widely used, with the skin test being the most popular. It is simple and quick to perform and carries little risk for the patient. The provocation test with food is different - because in the worst case, the patient can suffer a severe anaphylactic reaction. The disadvantage of the skin test is that the prerequisites must be right: it should be done with a perfect reagent, the patient should not have any skin problems and should not be taking any medication.

The skin test also often serves as a pre-test, the result of which is confirmed by in-vitro testing. In the in-vitro test, economic reality is a big

filtering factor. The patient is either tested for only a few allergens or must pay themselves if an extensive panel is to be covered.

The status quo: What are the weak points of allergy diagnostics globally, and how can they be improved?

CH: Tests that are performed live on the patient - such as skin tests - have the problem that the quality of the reagents used is indefinable. Allergens are often missing because they could not be extracted, or they are often contaminated. Cross-reactivities often arise that cannot be resolved. So standardisation is one of the main problems. A good example is the prick-to-prick test, where first a food is pricked, and then the patient's skin. Everyone knows that not all pineapples are the same, not all apples are the same. In-vivo tests are strongly influenced by factors such as medication and skin diseases like neurodermatitis, and this makes the results difficult to read and interpret.

In contrast, in-vitro testing is largely independent of patient-specific influences. Taking medication such as cortisone or antihistamines has no influence on the in-vitro test.

What would be the economic benefit if precise in-vitro allergy diagnostics such as MADx tests were to be promoted more?

CH: There are various studies on this that have been carried out by interest groups of the EU Parliament. For example, there is a study that states that 142 billion € could be saved annually if patients were diagnosed correctly from the beginning and subsequently treated correctly. Of course, we have to look at this critically, as these figures are based on model calculations that try to derive an economic damage retrospectively.

Essentially, there are two problems: People are not tested enough, and those who are tested often get an incomplete or wrong result. In the worst case, people are not treated at all or are even treated incorrectly. This causes direct damage to the health of the patient, but also great indirect damage to society through loss of work, reduced quality of life, and premature death.

Immunological diseases are divided into stages, and often there is a change of stage which is known as "progression" in medical terms. What starts as hay fever can develop into asthma. If you intervene in time, you can stop the jump to the next stage. But once you have reached that stage, there is no turning back, there is no medication or therapy.

It has been clear for over 40 years that molecular allergy diagnostics could solve many of these problems. There is greater standardisation, cheaper manufacture, and better clinical predictive power. The problem is that a large number of parameters are tested. What is usually tested with 3 or 4 parameters must be broken down molecularly here. At the moment, these parameters are still sold at a high price, and this is not affordable for health systems. Our goal as MADx is to make this technology, which has so far only been positioned for the absolute top segment, mainstream. Molecular allergy diagnostics should be cheaper, affordable for everyone and understandable for every doctor.

Why is it so much easier for companies like MADx to gain a foothold in Eastern European countries? On the other hand, what are the barriers in Western Europe and in Austria?

CH: In countries where the patient is self-paying, we clearly see that the decision is based on the best price-performance ratio. If an allergy test with 10 allergens costs almost as much as a test with 300 allergens, and the blood collection is even less invasive for the more extensive test, even a patient who is financially weak will, in case of doubt, opt for the test that offers them added value.

In more western countries like Austria, we are confronted with the health insurance problem. From an economic point of view, it is a loss for the doctor to attend to a complex allergy patient, because they have to attend to 10 patients per hour in order to make a profit. There is a lot of catching up to do in the health system. A rethink is needed here: If we focus more on diagnostic and therapeutic prevention in the future, it would save a lot of money in the medium term - but it will cost the system more in the short term.

A look into the future: Where will molecular allergy diagnostics go in the future? To what degree will precision medicine and patient-tailored allergy diagnostics become established? What will it take for that to happen?

CH: To establish precision medicine, we lack data above all. Prevalence studies may break the data down to allergen sources, but there is no data on combination with therapies - for example, which therapeutic approaches are suitable for which patients with specific molecular patterns. As MADx, we are trying to generate this data with our digital ecosystem, but we can't do it alone - this is where the whole industry has to work together.

In the future, we will probably completely move away from extract-based diagnostics, which are difficult to standardise, to molecular diagnostics. In molecular diagnostics, we will perhaps go one

step further and in future break down to epitopes, i.e., individual sub-areas of the protein, in order to predict precisely whether a patient is susceptible to severe reactions or not.

As MADx, we want to make precisely these tools suitable for mass use by medical professionals. We want to help doctors from other specialties to interpret findings correctly. Not every dermatologist is an allergy specialist, but of course they care for allergy patients. We must support these doctors with knowledge and efficiency, they should get a condensed and precise treatment suggestion from us. We don't want to replace the doctor, but we want to make their life as easy as possible.

In addition, through our consumer concepts, we want to try to pull the patient into the test cycle through low threshold offers. There will also be a lot of movement in the direction of telehealth in the near future - how much and how quickly depends on the geographical and social conditions. In emerging countries, it will be much quicker to implement because there are fewer strong lobbies that can block this development.

In the future, there will probably be standardised questionnaires that a patient can go through online. An algorithm will then decide which tests make sense for the patient, for example for allergies or other diseases. This way, no critical infrastructure is blocked, and after the first classification, another algorithm or a specialist can decide how to proceed with the patient. This is in everyone's interest, including the patient's - if only because of the time saved.

ABOUT

DR. CHRISTIAN HARWANEGG

studied Molecular Genetics at the University of Vienna, Austria. He joined a team of entrepreneurs in 1999 and graduated with a PhD in 2003. He has spent his entire professional education and career working in the development of all aspects of allergy testing in a multiplexed setup.

> "Our goal is to become the #1 allergy diagnostics provider."

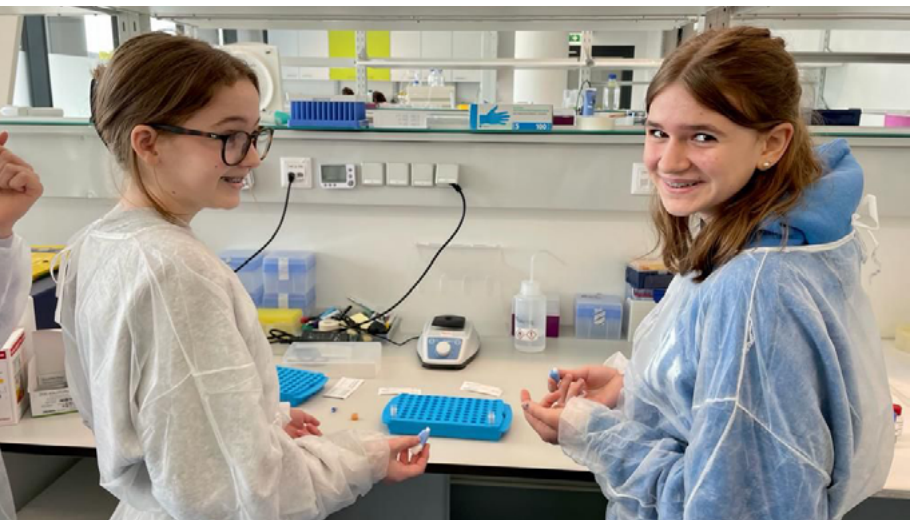
Wiener Töchtertag 2022

The Wiener Töchtertag ("Viennese Daughter's Day") is an annual event that gives young girls between the age of 11 and 16 the opportunity to experience work life at different companies from the technology, digitisation, crafts, and science sectors. This project has been instated 20 years ago, and within these 20 years, about 50,000 girls had the chance to visit different Viennese companies to learn more about jobs in these sectors.

This year, MADx participated in this event and invited ten girls to peek behind the curtains of a live science company at our headquarters in Vienna on April 28th, 2022.

Among other items on the agenda, our guests were able to learn about the differences between allergies and food intolerances, take a tour through the laboratory and learn about the production of allergen extracts, and had the option to take their own blood sample via finger prick for analysis.

In our lab, the girls were introduced to the different steps required to offer the entire value chain of allergy diagnostics: from producing test material to offering evaluation through the necessary software and hardware equipment.



At the end of the day, the girls received their own test results and were able to show off what they learned about the world of allergy diagnostics and MADx through a short quiz. The winner happily received a bookstore giftcard as her well-deserved prize.

MADx' first participation at the Wiener Töchtertag was a success, with ten girls visiting and learning more about our work. We are looking forward to participating again and expanding the program in 2023!

Event calendar

EUROPE 2022

DÜSSELDORFER ALLERGIE- UND IMMUNOLOGIETAGE

- 10. - 11.06
- Düsseldorf, Germany
- www.dait.nrw

31. JAHRESTAGUNG DER APPA

- 10. - 11.06
- Chemnitz, Germany
- www.appa-ev.de

EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

- 01. - 03.07
- Prague, Czech Republic
- www.eaaci.org

FORTBILDUNGSWOCHE FÜR PRAKTISCHE DERMATOLOGIE UND VENEROLOGIE

- 12. - 16.07
- Munich, Germany
- www.fortbildungswoche.de

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