

## Original Article

# HAZELNUT ALLERGY: A MULTI-FACED CONDITION WITH DEMOGRAPHIC AND GEOGRAPHIC CHARACTERISTICS

Ebo DG <sup>1</sup>, Verweij MM<sup>1, 2</sup>, Sabato V<sup>1</sup>, Hagendorens MM<sup>1, 2</sup>, Bridts CH<sup>1</sup>, De Clerck LS<sup>1</sup>

<sup>1</sup>Faculty of Medicine, Department of Immunology, Allergology, Rheumatology, University of Antwerp, Antwerpen, Belgium and Immunology, Allergology, Rheumatology, Antwerp University Hospital, Antwerpen, Belgium, <sup>2</sup>Faculty of Medicine, Department of Pediatrics, University of Antwerp, Antwerpen, Belgium and Pediatrics, Antwerp University Hospital, Antwerpen, Belgium

Correspondence and offprint requests to: Didier Ebo, E-mail: immuno@ua.ac.be

## ABSTRACT

Hazelnut (*Corylus avellana*) allergy varies from rather mild oral allergy symptoms to potentially life-threatening anaphylaxis and exhibits geographic and age-related variations. Severity of symptoms depends on the sensitisation profile of the patient and can partially be predicted using 'component-resolved diagnosis'. In our region (young) children predominantly exhibit sensitisation to hazelnut storage proteins Cor a 9 and Cor a 11 that is unrelated to birch pollen allergy and is generally associated with a more severe clinical outcome on consumption on raw and processed hazelnut. In contrast, adults predominantly present with an oral allergy syndrome due to an extensive cross-reactivity between the labile Cor a 1.04 and Bet v 1, the major allergen from birch (*Betula verrucosa*) pollen. In the absence of a cure, avoidance remains the key measure of effective management, particularly in those patients presenting with a severe form.

**Key words:** Allergy, Component resolved diagnosis (CRD), Cor a, hazelnut, IgE

## INTRODUCTION

Hazelnut constitutes an important and increasing cause of food sensitisation/allergy in children as well as in adults (1-4) with geographic and age-related variations regarding the severity of symptoms and depending on the sensitisation profile of the patient (5-10). This review intends to summarise the current knowledge of 2 well-established kinds of hazelnut

allergy, i.e. pollen-related and pollen-unrelated hazelnut allergy, in order to optimise diagnosis and management of patients. For a comprehensive approach of food allergy in general the reader is referred elsewhere (11).

## POLLEN-RELATED HAZELNUT ALLERGY

Pollen allergy constitutes an important major health problem that affects approximately 20% of the general population (12). Traditionally, patients suffer from seasonal rhinoconjunctivitis and/or asthma. However, over 50% of the patients with a pollen allergy also present a so-called pollen-related food allergy. The best-known representative of these pollen-related food allergies is the "birch-fruit-vegetable" syndrome that results from a cross-reactivity between the major allergen Bet v 1 from birch (*Betula verrucosa*) and its homologues in the implicated foods (5, 13, 14). In addition to traditional stone fruits, pit fruits and particular vegetables such as carrot and celery, allergy to tree nuts such as hazelnut can be related to birch pollen allergy. Actually, it has consistently been shown that birch pollen-related hazelnut allergy is predominantly observed in adults and is generally characterised by an oral allergy syndrome (OAS) in which patients generally present with local discomfort of the oropharyngeal cavity, although more generalised reactions are not excluded (7-9). The pathomechanism of pollen-related hazelnut allergy rests upon an extensive cross-reactivity between the labile Cor a 1.04 and Bet v 1. Table 1 summarises the most important hazelnut allergen components. The extent of sensitization towards Bet v 1 and Cor a 1.04 in the general population is currently unknown, but in our surveys the correlation between both sensitisation was over 0.92 (8) with a sensitisation to Bet v 1 being restricted to patients with birch pollen allergy (15). Another

protein capable to induce cross-reactivity between pollen and hazelnut is profilin, Bet v 2 in birch pollen (5, 6, 14, 16-18). In our own series sensitisation to profilin was almost absent in patients with an isolated birch or grass pollen allergy but was demonstrable in 5/25 patients with combined pollen allergy (birch + grass + weeds) (15). Anyhow, as monosensitisation to profilin in our region remains rare, its clinical relevance remains elusive but seems rather limited (9, 15, 19, 20).

## POLLEN-UNRELATED HAZELNUT ALLERGY

During the last decade it has emerged that hazelnut allergy can also occur without prior sensitisation to tree (birch) pollen. Unlike pollen-related hazelnut allergy, this condition is generally more severe with potentially life-threatening generalised reactions. It was initially described in adults from a Mediterranean non-birch endemic region (21-23). Unlike North European patients, these patients are not sensitised to Cor a 1.04 but appeared to react against the lipid transfer protein (LTP) Cor a 8, a member from the prolamin superfamily (22-25). Sensitisation to Cor a 8 was also described in a small series of 8 hazelnut allergic children in the Netherlands, a non-Mediterranean, birch-endemic region (26). However, this observation could not be confirmed by others (7, 8, 27). Alternatively, it was recently demonstrated that peach (*Prunus persica*) is the primary sensitizer to LTP from a large spectrum of botanically unrelated plant-derived foods including Cor a 8 from hazelnut (28-30). The limited sensitisation potential of Cor a 8 seems to relate with rapid lysosomal degradation during antigen processing and lack of dominant T cell epitopes (29).

A second member of the prolamins that was recently associated to more severe hazelnut allergy is the 2S albumin, Cor a 14 (22, 31). However clinical, demographic and epidemiological data on sensitisation to Cor a 14 remain limited.

Another group of plant allergens that was related to more severe hazelnut allergy is the superfamily of the cupins comprising the 11S legumine-like seed storage protein Cor a 9 and 7S vicilin Cor a 11. Actually, Beyer et al. (32) demonstrated reactivity to Cor a 9 in 12/14 patients with systemic reactions (mainly children), and, Hansen et al. (7) found sensitisation to Cor a 9 in four of seven Spanish patients with severe hazelnut allergy. Finally, it was shown that the sensitisation to Cor a 9 in our regions not only exhibits a distinct clinical pattern but also an age-related distribution, as reactivity to Cor a 9 was demonstrable in 11/17 pre-school children (median age 2 years), 3/6 schoolchildren and 1/6 adults with severe hazelnut allergy and in none of the 36 patients with an isolated OAS (8). Unlike Cor a 1.04 and Cor a 8, the exact sensitisation route for Cor a 9 remains elusive. However, it has been shown that sensitisation to Cor a 9 can appear in very young infants prior to tree pollen sensitization or pollen allergy, and independently from sensitisation to its homologues in legumes such as soy and peanut (33).

Sensitisation to Cor a 11 was first reported by Lauer et al. (27), who described IgE-binding to purified and recombinant Cor a 11 in approximately half of the tested adult population from a birch endemic region presenting with a

hazelnut-related OAS. However, this observation was not confirmed in a multi-centric study by Hansen et al. (7). In our series, 8/22 preschool children and 4/10 of the school children with systemic reactions to hazelnut were sensitised to Cor a 11. In contrast, sensitisation to Cor a 11 was only seen in 1/8 of the adults with a systemic reaction. Sensitisation to Cor a 11 was also found in 2 out of 6 preschool children but not in the school aged children or adults with an OAS. None of the birch pollen allergic patients without hazelnut allergy or healthy control individuals showed IgE reactivity to Cor a 11 (34). Hazelnuts contain multiple isoforms of oleosins that might also act as allergens (35).

## DIAGNOSIS

It's essential to differentiate between the aforementioned clinical kinds of hazelnut allergy in order to correctly advice on prognosis, risk management, avoidance measures and rescue medication. Theoretically, discrimination between these kinds of hazelnut allergy should rely upon history and a double-blind placebo controlled food challenge (DBPCFC), which is considered the gold standard to diagnose food allergy. However, DBPCFCs are hampered by several practical and ethical issues and do not demonstrate absolute predictive value (22, 36). Therefore, DBPCFC have failed to enter daily practice and are generally restricted to patient's suggestive histories but equivocal or negative test results. Alternatively, DBPCFC can be useful to establish individual threshold values of clinical reactivity, to predict clinical reactivity and to investigate clinically relevant co-sensitisation. These parameters are of utmost importance to guide dietary advice. For description of DBPCFC protocols for hazelnut the reader is referred elsewhere (18, 36-39).

By consequence, most physicians will rely upon quantification of specific IgE (sIgE) antibodies and skin tests as first measures to confirm their clinical suspicion. However, the performance of these tests has been repeatedly demonstrated to be far from absolute, with reasonably sensitivity and negative predictive value but low specificity and positive predictive value, particularly when applied to diagnose pollen-related hazelnut allergy (8, 9, 22, 37, 40). Actually, both tests frequently fail to discriminate between pollen allergic patients with hazelnut sensitisation and genuine pollen-related hazelnut allergy and are not at all predictive for clinical severity.

For quantification of sIgE, this problem was undoubtedly compounded by spiking the traditional sIgE method with a recombinant Cor a 1 (41). Moreover, it cannot fully be excluded that this spiking with Cor a 1 negatively affects the quantification of sIgE antibodies against components poorly represented in the native extract used in the traditional assays. The absence of potentially severe allergens like LTP in commercial hazelnut extracts was demonstrated by Akkerdaas et al. (42, 43). Actually, this study showed that correct diagnosis of hazelnut allergy by skin testing could be severely hampered due to extreme heterogeneous protein concentration and composition of hazelnut extracts.

Note that IgG4 antibodies to hazelnut have no diagnostic value in pollen-related hazelnut allergy (9). Actually,

quantification of IgG4 antibodies should be abandoned in the diagnostic approach of food allergy (44, 45).

During the last decades a new *in vitro* technique has entered the field of allergy diagnosis, that is, component-resolved allergy diagnosis (CRD). In contrast to traditional specific IgE (sIgE) assays, CRD does not rely upon whole extract preparations from native allergens but on quantification of sIgE antibodies to single protein components, purified from natural sources or obtained by recombinant techniques. It emerges that CRD can improve management of the allergic patient as it allows (to some extent) to discriminate between clinically significant and irrelevant sIgE result and to establish sensitisation patterns with particular prognostic outcomes (46). Although, CRD might facilitate correct diagnosis of hazelnut allergy, several issues should be kept in mind. First, quantification of Cor a 1.04 specific sIgE antibodies offers no advantage over the commonly used Cor a 1.04-spiked hazelnut assay in pollen-related hazelnut allergy, as it fails to discriminate between birch pollen allergic patients with and without hazelnut allergy (8), a phenomenon that also applies for other Bet v 1 homologues such as Mal d 1 from apple (*Malus domestica*) (47). A similar observation was done by Asero who demonstrated clinically irrelevant sensitisation to be common in LTP sensitive patients (30) and the level of Cor a 8 sIgE antibodies cannot be considered as absolutely predictive (48). Finally, it is of note that CRD by microarray involving quantification of sIgE to Cor a 1, Cor a 8, and Cor a 9 detected sensitisation to hazelnut in only 60% of our patients, indicating that further identification of offending allergens is mandatory to cover the spectrum of IgE reactivity against hazelnut (8).

Whether the diagnosis of hazelnut allergy might benefit from tests such as mediator release assays or flow-assisted basophil activation tests remains to be established and might relate to the type of hazelnut allergy (49-51). Perhaps, these tests might help to discriminate between pollen-related hazelnut sensitisation and genuine allergy, as demonstrated for apple (52).

## NATURAL COURSE AND THERAPEUTIC MANAGEMENT

The natural history of hazelnut sensitisation/allergy is unknown and remains to be assessed in comprehensive longitudinal studies but it has been demonstrated that the effect of birch pollen-specific immunotherapy is limited (53) or absent in birch pollen-related hazelnut allergy (54). Evidence is growing that oral tolerance induction through orally- or sublingually-administered gradually increasing doses of food might constitute an attractive approach to treat food allergic patients in the future (55, 56). However, to the best of our knowledge, there is currently only 1 randomised placebo-controlled double-blind sublingual immunotherapy study with a standardised hazelnut extract that demonstrates prolonged efficacy of this approach (57, 58). However, the study is small and results were currently not repeated by others. Therefore, today, avoidance remains the key measure to avert future reactions, particularly in patients demonstrating a severe hazelnut allergy. It is obvious that dietary recommendations should be adopted to the individual patient. Patients with severe and potentially life-threatening reactions require

absolute diets strictly avoiding the ingestion of (traces of) raw or processed hazelnut. In patients with a birch pollen-related hazelnut allergy avoidance measures might be less strict, as the responsible allergen component is thermolabile and will generally trigger only a mild OAS with symptoms confined to the oropharynx. Alternatively, it should be kept in mind that pollen-related hazelnut allergy in our regions is frequently associated with co-sensitization/allergy to other pit and stone fruits, whereas the pollen-unrelated form in our regions can be associated with sensitisation/allergy to other tree nuts and legumes such as peanut and soy (6, 59-61). This should be emphasised in the dietary advice towards the patient. Prescription and recommendations about use of rescue medication (auto-injectable epinephrine, antihistamines,  $\beta$ -2 agonists, glucocorticosteroids) is mandatory, but (too) frequently forgotten (3).

## CONCLUSION

Hazelnut allergy is a double-faced condition with distinct clinical outcomes and particular sensitisation patterns that display age and geographical characteristics.

In adults from birch endemic regions, hazelnut allergy predominantly presents as a traditional pollen-associated mild OAS that relies on a cross-reactivity between Cor a 1 and Cor a 2 from hazelnut and the homologues proteins in birch pollen, i.e. Bet v 1 and Bet v 2. In contrast, adults from regions where birch is not endemic generally demonstrate a more severe condition that seems to originate from a cross-reactivity between the lipid transfer protein Cor a 8 from hazelnut and its counterpart Pru p 3 from peach.

Children generally demonstrate severe hazelnut allergy that results from a primary sensitisation to cupins, a plant-allergen family that comprises the legumine-like Cor a 9 and vicilin Cor a 11. Moreover, our group has demonstrated that sensitisation to Cor a 9, unlike Cor a 11, can already appear at the extreme young age of some months.

Alternatively, the clinical outcome as well as potential age and geographic distribution for the more recently identified components such as the 2S albumin Cor 14 and oleosins remain greatly to be established.

Theoretically, discrimination between these kinds of hazelnut allergy should rely upon history documented by a DBPCFC, which is considered the gold standard to diagnose food allergy. However, the DBPCFC has still not entered into the mainstream diagnosis as its application is hampered by different practical and mostly ethical issues. Alternatively, the predictive value of quantification of specific IgE antibodies and skin tests for hazelnut have been repeatedly demonstrated to be far from absolute. Although, component resolved allergy diagnosis might facilitate correct diagnosis of hazelnut allergy, further identification of offending allergens seems mandatory to cover the spectrum of IgE reactivity against hazelnut.

Avoidance remains the sole manner to avert potentially life-threatening reactions, particularly in patients demonstrating a hazelnut allergy independent of pollen sensitisation.

**CONFLICT OF INTEREST:** None declared.

Table

| Allergen | Name                                     | MW (kDa) | Food allergen | Homologues                           | Clinical relevance | Ref                      |
|----------|------------------------------------------|----------|---------------|--------------------------------------|--------------------|--------------------------|
| Cor a 1  | Pathogenesis-related protein, PR-10      | 17       | Yes           | Bet v 1                              | > OAS              | (5-9)                    |
| Cor a 2  | Profilin                                 | 14       | Yes           | Bet v 2                              | > OAS              | (5;6;14;16-18)           |
| Cor a 8  | Non-specific lipid transfer protein 1    | 9        | Yes           | Pru p 3, Jug r 3                     | > Severe           | (22-26) <sup>1</sup>     |
| Cor a 9  | 11S seed storage globulin (legumin-like) | 40       | Yes           | Ara h 3, Jug r 4, Gly m 6, Ana o 2   | Severe             | (7;8;32;33) <sup>2</sup> |
| Cor a 10 | Luminal binding protein                  | 70       | No            |                                      |                    |                          |
| Cor a 11 | 7S seed storage globulin (vicilin-like)  | 48       | Yes           | Ara h 1, Jug r 2, Ana o 1,           | Severe             | (27) <sup>3</sup>        |
| Cor a 12 | Oleosins                                 | 17       | Yes           | Ara h 10, Ara h 11, Ses i 1, Ses i 5 | Severe?            | (35)                     |
| Cor a 13 |                                          | 14-16    | Yes           |                                      |                    |                          |
| Cor a 14 | 2S albumin                               | 15-16    | Yes           | Ara h 2                              | Severe             | (22;31)                  |

Cor a: *Corylus avellana* (hazelnut), Ara h: *Arachis hypogaea* (peanut), Jug r: *Juglans regia* (walnut), Gly m: *Glycine max* (soy), Bet v: *Betula verrucosa* (birch), Ses i: *Sesamum indicum* (sesame), Pru p: *Prunus persica* (peach), Ana o: *Anacardium occidentale* (cashew).

<sup>1</sup>Data of Flinterman et al. could not be reproduced by others. <sup>2</sup>In the series of Verweij et al. sensitisation to Cor a 9 was demonstrable before overt intake of hazelnut. <sup>3</sup>Sensitisation to Cor a 11 was also demonstrated by Verweij et al (in review).

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