

Young infants with atopic dermatitis can display sensitization to Cor a 9, an 11S legumin-like seed-storage protein from hazelnut (*Corylus avellana*)

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Allergy to hazelnut (*Corylus avellana*) can be severe and occur at young age. Atopic dermatitis (AD) can involve sensitization to various foods. The objective is to investigate the pattern of hazelnut sensitization in infants with AD. Sera of 34 infants all under 1 year of age and suffering from AD were selected according to prior specific IgE results. Twenty-nine infants were sensitized to traditional food allergens, five were not. From the 29 infants with a sensitization to at least one food allergen, 20 demonstrated IgE reactivity to hazelnut. All sera were analyzed with the allergen microarray immunoassay (ImmunoCAP ISAC). Twelve (60%) of the children with IgE reactivity to hazelnut demonstrated sensitization to Cor a 9, the 11S legumin-like seed-storage protein from hazelnut. In these infants, no sensitization to Cor a 1, the homologue of the major birch pollen allergen Bet v 1 (*Betula verrucosa*), or the lipid transfer protein (Cor a 8) from hazelnut was demonstrable. Half of the children sensitized to Cor a 9 demonstrated IgE reactivity to its homologue in peanut (*Arachis hypogaea*; Ara h 3) from which five were also sensitized to Gly m 6 from soy (*Glycine max*). None of the infants with AD without IgE reactivity to hazelnut demonstrated sensitization to Cor a 1, 8, or 9. In conclusion, young infants with atopic dermatitis sensitized to hazelnut can already display IgE reactivity to Cor a 9, a potentially dangerous hazelnut component. The mechanism(s) of this early sensitization and its clinical significance remain elusive.

Marjoke M. Verweij^{1,2}, Margo M. Hagendorens^{1,2}, Kathleen J. De Knop¹, Chris H. Bridts¹, Luc S. De Clerck¹, Wim J. Stevens¹ and Didier G. Ebo¹

¹Department of Immunology – Allergology – Rheumatology, Faculty of Medicine, University of Antwerp, Belgium, ²Department of Pediatrics, Faculty of Medicine, University of Antwerp, Belgium

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Wim J. Stevens, University of Antwerp, Department of Immunology – Allergology – Rheumatology, Universiteitsplein 1, B-2610 Antwerpen, Belgium
Tel.: ++32 3 265 25 95
Fax: ++32 3 265 26 55
E-mail: immuno@ua.ac.be

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Allergy to hazelnut (*Corylus avellana*) is an important health issue with a rising prevalence (1). Different sensitization patterns to hazelnut with distinct symptomatology have recently been identified [for review: (2)]. A mild oral allergy syndrome is predominantly seen in adults from birch-endemic areas and relies upon a cross-reactivity between Cor a 1 and Bet v 1, the major allergen from birch pollen (*Betula*

verrucosa) (3–4). In contrast, more severe reactions can occur in adults from non-birch-endemic regions with a sensitization to the hazelnut lipid transfer protein Cor a 8 (4–6). Recently, systemic hazelnut allergy has also been described in young children from a birch-endemic region with a sensitization to the lipid transfer protein Cor a 8 (7). In addition, Beyer et al. (8) have suggested that severe pollen-unrelated hazelnut allergy in patients, most of whom were children, might result from sensitization to the 11S legumin-like seed-storage protein Cor a 9. However, the exact moment

Abbreviations: AD, atopic dermatitis; CRD, component resolved diagnosis; CCD, cross-reactive carbohydrate determinants; OAS, oral allergy syndrome; sIgE, specific IgE.

and mechanisms for sensitization to these pollen-unrelated hazelnut components in children remain to be disentangled, particular as it has been reported that children can present severe reactions already on the first known exposure (7, 9).

Atopic dermatitis (AD) is traditionally considered as the primary manifestation of an atopic status that can involve sensitizations to various food allergens (10). Most frequently involved foods are hen's egg and cow's milk, but broader sensitization profiles involving wheat, soy, potato, peanut, and several tree nuts have been described (11–14). However, sensitization patterns to different hazelnut components in children with AD have not been published yet.

In this study, we investigate the hazelnut sensitization profile of young children under 1 year of age presenting with AD, as this could help to identify children at risk for future severe hazelnut allergy. For this purpose, a microarray was used as it creates the opportunity to establish individual sensitization Pattern and risk profiles in a single analysis with minute amounts of serum (15, 16).

Methods

Population

Sera of children under 1 year of age with AD were selected according to prior specific IgE quantifications. Twenty-nine of them demonstrated a sensitization to at least one of the common food allergens (cow's milk, hen's egg, wheat, soy, potato, and peanut). Twenty infants (M: 15, F: 5; median (range) age 9 (4–11) months) were known to present a sensitization to hazelnut as revealed by a positive sIgE to hazelnut, whereas nine infants (M: 9, F: 0; median (range) age 7 (5–11) months) had no sensitization to hazelnut (negative sIgE result). In the remaining five infants (M: 3, F: 2; median (range) age 7 (5–12) months), no sensitization to the aforementioned traditional food allergens or hazelnut was demonstrable. For ethical reasons, in these young infants no double-blind placebo-controlled food challenges were performed.

Total and sIgE by ImmunoCAP

Total IgE and sIgE to hazelnut, nCor a 9, cow's milk, hen's egg, wheat, soy, potato, and peanut were analyzed with ImmunoCAP FEIA (Phadia, Uppsala, Sweden) according to the manufacturer's recommendations. Values of sIgE ≥ 0.35

kUA/l were considered positive. Note that nCor a 9 coupled to the ImmunoCAP is the same antigen as spotted on the microarray.

Microarray

To determine sIgE against allergen components, the allergen microarray immunoassay, on which 103 components are spotted, (ImmunoCAP ISAC, Phadia, Uppsala, Sweden), was used as recommended by the manufacturers and recently described elsewhere (17). Briefly, microarray reaction sites were incubated with 20 μ l of undiluted patients' serum for 2 h to capture possible allergen-specific IgE antibodies by their corresponding allergen. Subsequently, the microarray slides were rinsed and washed with buffer solution to remove unbound serum sIgE. After drying, complexes of allergen-bound sIgE were stained with a secondary, fluorescence-labeled anti-human IgE for 1 h at room temperature protected from light. After a second rinsing and washing procedure, the obtained fluorescence signals were scanned using a confocal laser scanner (LuxScan 10K, CapitalBio, Beijing, China). Analysis of the corresponding digitized microarray image data was performed with ImmunoCAP ISAC software, and image information was transformed into numerical data according to calibration sera of known sIgE content. Numerical data were expressed as ISAC Standardized Units (ISU/l), and the decision threshold was set at 0. Allergen components were denoted by their accepted taxonomic name preceded by 'n' for isolated natural (glycolyzed) proteins or 'r' for recombinant proteins.

Statistics

Results were expressed as median (range). Non-parametric tests were used where appropriate. SPSS 16 software was applied for data analyses. Fisher's exact testing was performed to compare frequencies.

Results

From Table 1, it emerges that children with hazelnut sensitization show significantly more (co)sensitization or cross-sensitization to peanut, soy, and wheat. Results of the microarray are summarized in Fig. 1. Twelve (60%) of the hazelnut-sensitized infants demonstrated IgE reactivity to nCor a 9, whereas none of the hazelnut-sensitized infants reacted to rCor a 1 or rCor a 8 (Table 2). All infants without sensitization to hazelnut demonstrated negative sIgE

Table 1. Individual data of IgE sensitization by ImmunoCAP to potential cross-reactive plant derived food allergens

	Peanut (f13)	Soy (f14)	Wheat (f4)	Potato (f35)
Infants with hazelnut sensitization				
pt 1	22.1	21.4	63.4	24.3
pt 2	14.6	6.75	100	13.7
pt 3	96.3	8.1	9.18	10.1
pt 4	>100	23.8	4.33	0.36
pt 5	3.13	<0.35	1.99	28.3
pt 6	0.41	<0.35	NA	NA
pt 7	1.61	0.47	9.63	NA
pt 8	2.66	0.47	26.1	NA
pt 9	8.07	3.73	1.21	4.2
pt 10	0.81	<0.35	<0.35	0.65
pt 11	1.66	<0.35	<0.35	3.18
pt 12	>100	2.38	<0.35	NA
pt 13	13.1	<0.35	0.57	<0.35
pt 14	<0.35	<0.35	<0.35	<0.35
pt 15	<0.35	<0.35	2.01	15.2
pt 16	<0.35	<0.35	<0.35	0.48
pt 17	<0.35	NA	NA	NA
pt 18	NA	<0.35	<0.35	3.22
pt 19	0.35	NA	11.1	<0.35
pt 20	<0.35	1.91	3.63	21.6
Infants without hazelnut sensitization				
pt 21	<0.35	<0.35	0.36	<0.35
pt 22	NA	<0.35	<0.35	0.85
pt 23	<0.35	<0.35	<0.35	2.00
pt 24	<0.35	<0.35	<0.35	0.44
pt 25	<0.35	<0.35	1.64	0.85
pt 26	<0.35	<0.35	NA	NA
pt 27	<0.35	<0.35	<0.35	0.75
pt 28	<0.35	<0.35	<0.35	1.29
pt 29	<0.35	<0.35	<0.35	<0.35

Specific IgE results are expressed in kUA/l.
Pt, Patients; NA, not available.

results to the three hazelnut components spotted on the microchip. Figure 2 displays the correlation between sIgE to Cor a 9 on the microarray and sIgE hazelnut by traditional ImmunoCAP. From this figure, it emerges that sIgE to Cor a 9 is highly related to sIgE hazelnut ($r = 0.88$, $p < 0.001$). Except for one, all Cor a 9-positive sera spotted on the microarray, had a sIgE to hazelnut exceeding 5.5 kUA/l, whereas all sIgE to hazelnut for the Cor a 9-negative sera were < 2.0 kUA/l. To confirm the Cor a 9 microarray data, sera were also analyzed by a singleplexed ImmunoCAP assay coated with the same nCor a 9 component as used in the microarray. This comparative analysis demonstrated a high correlation ($r = 0.91$, $p < 0.001$).

Next to nCor a 9, the microarray contains three other 11S legumin-like seed-storage proteins, i.e., nAra h 3 from peanut (*Arachis hypogea*), nGly m 6 from soy (*Glycin max*), and rAna o 2 from cashew (*Anacardium occidentale*). Figure 1 displays the percentages of positive results for these different components. Sensitization to these legumin-like proteins was restricted to the infants sensitized to nCor a 9, except for one infant with a sensitization to nAra h 3 but not to nCor a 9. Actually, half of the patients sensitized to nCor a 9 demonstrated IgE reactivity to nAra h 3. Five of these six nAra h 3-sensitized infants also demonstrated a positive sIgE result to nGly m 6 from soy. Only one nCor a 9-sensitized infant showed IgE reactivity to rAna o 2.

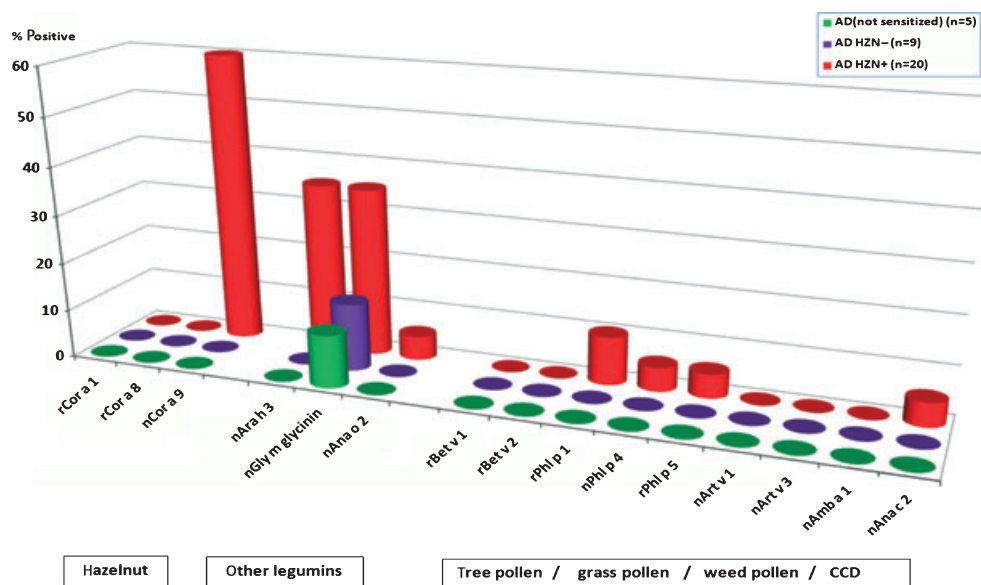


Fig. 1. Percentages of positive sIgE results by ISAC microarray for infants with (red) or without (blue) hazelnut sensitization and infants without any food sensitization (green). CCD, cross-reactive carbohydrate determinants; Bet v 2, birch profilin.

Table 2. Individual results from infants with hazelnut sensitization

	ISAC (ISU/I)						CAP (kUA/I)				
	rCor a 1	rCor a 8	nCor a 9	nAra h 3	nGly m 6	rAna o 2	Total IgE	Hazelnut	nCor a 9	rCor a 1	rCor a 8
pt 1	0	0	22.85	4.34	5.54	0	2135	>100	>100	<0.35	NA
pt 2	0	0	13.22	1.13	0.68	0	1858	>100	>100	NA	NA
pt 3	0	0	6.75	1.38	3.82	0	464	94.8	62.8	<0.35	<0.35
pt 4	0	0	2.68	2.13	2.76	0.77	1028	64.1	23.4	NA	<0.35
pt 5	0	0	1.84	0.47	0	0	1228	64.9	35	NA	<0.35
pt 6	0	0	1.73	0	0	0	61	13.8	6.77	NA	NA
pt 7	0	0	1.73	0	0	0	317	5.53	1.57	<0.35	<0.35
pt 8	0	0	1.06	0	0	0	156	5.65	2.88	<0.35	<0.35
pt 9	0	0	0.45	1.11	0.68	0	145	13.9	5.53	NA	NA
pt 10	0	0	0	0	0	0	39	1.01	0.5	NA	<0.35
pt 11	0	0	0	0	0	0	223	1.93	0.37	NA	<0.35
pt 12	0	0	0	0.58	1.3	0	404	0.83	1.16	NA	NA
pt 13	0	0	0	0	0	0	535	0.43	<0.35	<0.35	<0.35
pt 14	0	0	1.16	0	0	0	516	9.4	3.18	<0.35	NA
pt 15	0	0	0.88	0	0	0	247	13.8	6.28	NA	NA
pt 16	0	0	0.64	0	0	0	7	0.71	0.38	NA	NA
pt 17	0	0	0	0	0	0	55	0.77	<0.35	<0.35	<0.35
pt 18	0	0	0	0	0	0	28	0.44	<0.35	<0.35	<0.35
pt 19	0	0	0	0	0	0	60	0.52	<0.35	<0.35	NA
pt 20	0	0	0	0	0.39	0	161	2.12	<0.35	<0.35	NA

Pt, Patients; NA, not available.

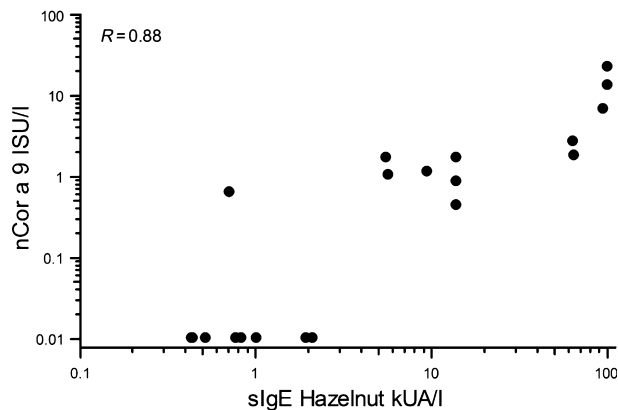


Fig. 2. Correlation between sIgE to nCor a 9 by ISAC microarray and sIgE to hazelnut by ImmunoCAP in the hazelnut-sensitized infants ($n = 20$).

As expected, sensitization to pollen in these young infants was rare. No sensitization to the major birch pollen allergen rBet v 1, weed pollen (*Artemisia vulgaris* and *Ambrosia artemisiifolia*), was found and only two infants were sensitized to grass pollen (*Phleum pratense*). No sensitization to profilin was found as assessed by the different representatives from the profilin family (rBet v 2 from birch pollen, rPhl p 12 from grass pollen, nOle e 2 from olive, rMer a 1 (*Mercurialis annua*) from Annual Mercury, and rHev b 8 (*Hevea brasiliensis*) from latex) spotted on the microarray. Only one patient demonstrated sensitization to cross-reactive carbohydrate determi-

nants (CCD) as revealed by a positive bromelain (nAna c 2: *Ananas comosus*) result (Fig. 1). No IgE seroreactivity was demonstrable to two other potential glycomarkers, i.e., nOle e 1 from olive (*Olea europaea*) and nApi m 1 from honeybee (*Apis mellifera*).

Discussion

The most striking observation of this study is that the majority of our young infants suffering from AD with a sensitization to hazelnut are sensitized to Cor a 9.

The exact route(s) of sensitization to Cor a 9 from hazelnut remain(s) highly elusive. As expected (7, 18), our infants were not sensitized to pollen that could have caused a cross-reactivity between Cor a 9 and its homologues component in pollen. Allergy to hazelnut can also occur independently from a prior pollen allergy. These sensitizations can occur primary to hazelnut or could eventually result from a cross-sensitization between hazelnut allergens and their homologues in other nuts or legumes such as peanut and soy (19, 20). Although parents in our series were not aware of their infants ever having consumed tree nuts (including hazelnut), peanut or soy, inadvertent ingestion cannot completely be excluded, as these allergens are difficult to avoid because of their possible presence in many other food products. Moreover, exposure to these foods might even have occurred through breastfeeding

(22, 23) or *in utero* (23). Anyhow, our data indicate that sensitization to Cor a 9 can occur independently from sensitization to its homologues in peanut and soy, as less than half of our patients demonstrated IgE reactivity to Ara h 3 or Gly m 6.

In addition to sensitization through inhalation and ingestion, a third potential route for sensitization might be through the skin (24, 25), especially as atopic dermatitis is characterized by epidermal barrier dysfunction resulting in a higher exposure to allergens (10, 26). As hazelnut oil and other tree nuts or peanut derived oils are frequently used in cosmetic products such as body cream and bath oil for their hydrating effect (27), children with AD might be more at risk for sensitization through skin contact.

Although hazelnut lipid transfer proteins have been identified as an important allergen in children with severe hazelnut allergy in a birch-endemic region (7), no IgE reactivity to Cor a 8 was demonstrable in our patients.

It is obvious that the finding of hazelnut sensitization in young infants with AD constitutes a clinical challenge. Although there was no clinical history of overt hazelnut allergy, for several reasons, we considered strict avoidance of hazelnut and related nuts/peanut as an imperative measure of the dietary advice. First, we cannot exclude that the intake of hazelnut could have a deleterious effect on the skin lesions of our patients (28). Second, it has been suggested that sensitization to Cor a 9 can be associated with severe hazelnut-induced anaphylaxis (8). Moreover, we recently observed sensitization to Cor a 9 in 11 of 20 young children (median age 2, range 11 months – 6 years) with severe hazelnut allergy (De Knop et al., manuscript submitted). Third, almost all cases sensitized to Cor a 9 demonstrated an sIgE hazelnut result exceeding the 75th percentile value of patients with established hazelnut allergy (29). Therefore, to gain further insights into the clinical relevance and prognosis of our observations we intend to follow these children longitudinally.

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 sensitization to hazelnut in 'only' 60% of our patients identified as hazelnut sensitized by a traditional hazelnut sIgE assay. Although we cannot establish the exact reason(s) for this discrepancy, we hypothesize that this might be attributed to the fact that the three components spotted onto the biochip do not cover the entire IgE profile of hazelnut. Therefore, it is anticipated that adding additional components, such as Cor a 11, to the microchip

will optimize the performance of the assay. An attractive alternative explanation for the positive sIgE hazelnut results without Cor a 9 sensitization could be sensitization to cross-reactive compounds such as profilins or CCD. However, this seems highly unlikely, as sensitization to these compounds in our regions generally results from sensitization to pollen (30). In our series, sIgE results for pollen, profilin, and CCD were virtually all negative. Also unspecific binding to the solid phase owing to high total IgE seems unlikely, as the highest total IgE value in Cor a 9-negative but hazelnut-sensitized infants was 535 kU/l (data not shown).

In conclusion, we present a group of infants less than 1 year of age with AD and a sensitization to hazelnut of which 60% are sensitized to Cor a 9, a potentially dangerous hazelnut component. The exact moment and mechanisms for this early sensitization remain to be disentangled.

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