

Letter to the Editor

Clinical reactivity to hazelnut in children: Association with sensitization to birch pollen or nuts?

To the Editor:

In areas where birch trees are endemic, hazelnut allergy is often the result of primary sensitization to cross-reactive birch pollen allergen Bet v 1, usually resulting in mild oral allergy syndrome (OAS) in both adults and children.^{1,2} On the other hand, sensitization to hazelnut in early childhood has been related to sensitization to other tree nuts and peanut,^{3,4} which can all cause serious reactions.⁵ Children can be sensitized to hazelnut at an early age.³ Remarkably, a large proportion has never to their knowledge ingested hazelnut, and most allergic reactions to nuts in childhood occur after the first known exposure.⁶

This is the first study to determine the clinical relevance of hazelnut sensitization and eliciting doses (EDs) in childhood by double-blind placebo-controlled food challenge (DBPCFC). Furthermore, we investigated the relation between hazelnut allergy and sensitization to birch pollen and other species of nut and peanut.

Twenty-eight sensitized children (8 female, 20 male; age 4-16 years) with suspected allergy to hazelnut were recruited. All children were atopic, with atopic dermatitis the most frequently reported condition (86%). Sixteen children (57%) had seasonal rhinoconjunctivitis. Asthma-related symptoms were reported by 13 children (47%).

Sensitization was re-evaluated before DBPCFC by a skin prick test (SPT) with commercial hazelnut extract (ALK-Abelló, Nieuwegein, The Netherlands) and specific IgE levels using the CAP system FEIA (Pharmacia Diagnostics, Uppsala, Sweden) to hazelnut, birch pollen, almond, pecan, walnut, Brazil nut, pistachio, cashew, and peanut.

Double-blind placebo-controlled food challenges were performed as described previously,⁷ but not in the tree pollen season between mid-February and mid-June. Briefly, the challenge was composed of 9 portions of defatted hazelnut flour in series: 10 µg, 100 µg, 500 µg, 1 mg, 10 mg, 100 mg, 300 mg, 1 g, and 3 g (protein content, 15.5%; kindly provided by the Food Allergy Research and Resource Program, University of Nebraska). Four placebos were randomly interspersed by the pharmacist to complete the procedure in 1 day. The last dose was unblind and consisted of 10 hazelnuts (5 g; approximately 635 mg protein), because this amount could not be masked in edible portions for children. The challenge was only discontinued after the occurrence of an objective reaction.

Sixteen children (57%) did not show any reaction on hazelnut ingestion during the challenge procedure. In 12 children (43%), hazelnut allergy was confirmed by challenge. Doses as large as 1 mg (0.16 mg protein) were tolerated by all children (Table I). Four children (4/12; 33%) reported only OAS without developing objective symptoms at doses starting from 10 mg. One child (#17) refused further portions after aggravating symptoms of

OAS at 3 subsequent doses. These children with only OAS were all sensitized to birch pollen. The interval between ingestion and OAS was always less than 10 minutes.

Eight children (8/12; 67%) developed an objective reaction to hazelnut, such as systemic urticaria, rhinoconjunctivitis, vomiting, and dyspnea. ED for objective reactions ranged from 300 mg to 10 hazelnuts. In 5 children, the objective reactions were preceded by OAS on previous doses (100 mg to 3 g). In 3 children, OAS and objective symptoms developed on the same dose. Late reactions (as long as 24 hours after DBPCFC) were not reported. Three of the children with an objective reaction had low or undetectable birch pollen-specific IgE (<0.35-0.5 international kilounits allergen-specific IgE per liter [kU_A/L]), as well as grass pollen-specific IgE (<0.35-1.0 kU_A/L).

Skin prick test reactivity was significantly different between children without hazelnut allergy, children with only OAS, and children with objective symptoms; the latter group had the highest SPT reactivity. Specific IgE to hazelnut, but also to other species of nut, was significantly higher in children with objective reactions compared with children without objective reaction (children with only OAS or children without any reaction; $P < .05$ for all nuts, except for peanut, $P = .205$). Children with objective reactions were sensitized to more species of nuts (median, 6; range, 5-6) than children with only OAS (median, 4.5; range, 0-6) or no reaction (median, 2.5; range, 0-6). IgE reactivity to cross-reactive carbohydrate determinants of glycoproteins was determined in all children using RAST.⁸ This was negative in all but 1 patient (#23; data not shown) and was not associated with the type of reaction.

Challenges are an important tool in diagnosing food allergy.⁹ In this study, fewer than half of the children with sensitization to hazelnut appeared to be allergic to hazelnut. Moreover, challenges with increasing doses of hazelnut are the only way to determine ED. Doses as large as 1 mg hazelnut flour were tolerated by all children. The ED for OAS (≥ 10 mg; 1.6 mg protein) and for objective symptoms (≥ 300 mg; 46.5 mg protein) were in line with previous studies on hazelnut allergy in adults.¹⁰⁻¹² Similar EDs for objective symptoms to peanut were described in a comparable study in peanut-sensitized children: 100 mg peanut flour (50 mg protein).⁷ Although ED for hazelnut appeared to be the same in children and adults, children experienced more objective reactions than adults from our hospital (8/12, 67%, vs 2/29, 6.9%).¹⁰ It is unlikely that this is the result of a selection bias because the referral area is similar.

In our study, children with only OAS were all sensitized to birch pollen. In contrast, 3 of the children with additional objective symptoms to hazelnut had low or even undetectable birch pollen-specific IgE. This suggests a nonpollen-related route of sensitization to hazelnut in at

TABLE I. Sensitization to hazelnut, pollen, and other species of nut, and the results of DBPCFC per individual (n = 28)

		Hazelnut		Pollen*		Other species of nut and peanut*								DBPCFC Hazelnut			
No.	Age	IgE*	SPT†	Grass	Birch	Almond	Pecan	Walnut	Brazil	Pistachio	Cashew	Peanut	Symptoms‡	ED OAS	ED objective		
	(y)													(mg)	(mg)		
1	8	9	4	100	100	1	1	1	1	4	2	10	None	—	—		
2	9	2	6	49	76	0	0	0	0	0	0	4	None	—	—		
3	14	1	7	100	56	1	0	0	0	1	0	1	None	—	—		
4	8	4	4	100	100	0	—	0	—	1	0	15	None	—	—		
5	16	1	4	1	0	0	0	0	1	0	0	87	None	—	—		
6	14	26	2	18	39	19	1	0	2	20	20	100	None	—	—		
7	7	1	5	0	27	0	0	0	0	3	3	9	None	—	—		
8	4	0	8	0	0	0	—	0	—	—	4	0	None	—	—		
9	4	1	2	21	53	0	1	1	0	6	3	12	None	—	—		
10	6	0	3	0	0	0	0	0	0	4	4	1	None	—	—		
11	7	4§	5	7	100	1	1	1	1	6	3	8	None	—	—		
12	5	11	2	58	100	7	6	4	8	100	100	48	None	—	—		
13	4	1	2	68	0	0	0	0	1	1	2	2	None	—	—		
14	7	1	2	24	2	0	0	0	1	3	3	3	None	—	—		
15	6	4	5	100	100	0	1	0	1	1	0	1	None	—	—		
16	4	0	4	0	0.4	0	0	0	0	0	0	3	None	—	—		
17	12	8§	8	7	51	1	36	26	3	6	5	4	OAS	100	—		
18	4	2	6	26	27	3	3	3	2	5	2	7	OAS	>3000	—		
19	10	1	4	55	80	0	0	0	1	41	27	25	OAS	10	—		
20	5	1	7	2	3	0	0	0	0	0	0	0	OAS	>3000	—		
21	4	16	11	32	9	3	2	1	7	10	8	40	OAS, ap, vom	>3000	>3000		
22	6	4§	7	3	35	1	22	14	0	21	28	66	OAS, urt	100	>3000		
23	8	45	12	60	100	11	32	23	10	56	59	52	OAS, rc, ap, vom	3000	>3000		
24	13	20	10	34	62	9	7	4	—	18	15	100	OAS, urt, ap	100	>3000		
25	4	38§	17	1	0	2	22	22	3	6	6	3	OAS, ap, vom	100	300		
26	8	48	17	7	100	7	13	12	18	27	27	50	OAS, ap, vom	100	3000		
27	6	27	7	0	0.5	0	17	4	10	1	6	2	OAS, urt, rc, bro	>3000	>3000		
28	6	55	10	0	0	12	3	1	37	100	100	66	OAS, ap, dia	>3000	>3000		

*Specific IgE in kU_A/L; 0: <0.35; 100: >100.

†SPT diameter in millimeters.

‡Symptoms: *ap*, abdominal pain; *bro*, bronchoconstriction; *dia*, diarrhea; *rc*, rhinoconjunctivitis; *urt*, urticaria; *vom*, vomiting.

§Individual with allergic reaction to hazelnut by history.

least some of the children from areas where birch trees are endemic.

In particular, children with objective reactions to hazelnut had high levels of specific IgE to other nuts. The differences in sensitization to nuts between children with and without objective reactions to hazelnut did not appear to be explained by cross-reactive carbohydrate determinant reactivity. Atopic parameters such as total IgE levels and the scoring of atopic dermatitis were similar (data not shown); hence, this does not explain the differences in sensitization either. Although we did not investigate the clinical relevance of all nuts and the history did not provide information on previous exposure to most nuts, avoidance of all nuts may still be advisable in children with objective reactions to hazelnut. For future preventive and therapeutic strategies, it would be interesting

to investigate which major allergens are responsible for the primary sensitization in children with objective reactions to hazelnut.¹³

Our data indicate that sensitization to hazelnut is not clinically relevant in about half of the children. OAS was reported by all children with a reaction to hazelnut, at doses starting from 10 mg. Additional objective symptoms were observed in at least 67% of the reactions. These objective reactions to hazelnut were not always accompanied by sensitization to birch pollen, but always by sensitization to other nuts and peanut. This suggests that the route of clinically relevant sensitization to hazelnut in children, in an area where birch trees are endemic, can be nonpollen-related.

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