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Diagnostic value of hazelnut allergy tests including rCor a 1 spiking in double-blind challenged children

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Abstract

Background The diagnostic value of hazelnut allergy tests in double-blind challenged children is largely unknown. The aim of this study was to analyze the performance of current diagnostic tests for hazelnut allergy in children and the effect of spiking.

Methods Data of 151 children who underwent a double-blind placebo-controlled food challenge for hazelnut were analyzed. The positive predictive value and negative predictive value (PPV/NPV) of level of specific IgE (sIgE) for hazelnut, the influence of rCor a 1 spiking of the ImmunoCAP, and size of the skin prick test (SPT) for hazelnut were determined, also in relation to the severity of the hazelnut allergy. Reported accidental ingestion leading to an allergic reaction to hazelnut was also analyzed in relation to hazelnut allergy.

Results Specific IgE ≥ 0.35 kU_A/l for hazelnut was a moderate predictor for hazelnut allergy. The spiking decreased the PPV from 41% to 38% and increased the NPV from 91% to 100% for sIgE ≥ 0.35 kU_A/l. The maximum reached PPV was 73% for sIgE cutoff of 26 kU_A/l. Level of sIgE before spiking was significantly different between different grades of severity and was lost after spiking. Skin prick test was a better predictor for hazelnut allergy and severity than the level of sIgE. A history of accidental ingestion leading to an allergic reaction to hazelnut had a predictive value of 59% for hazelnut allergy.

Conclusions This study showed a good NPV of diagnostic tests for hazelnut allergy in children which further improved by rCor a 1 spiking. However, the PPVs are moderate and decreased by spiking.

Hazelnut allergy is often associated with other manifestations of the atopy syndrome (1–3) and accounts together with other tree nuts and peanut for >80% of fatalities caused by food allergy (4). Patients with a hazelnut allergy are advised to follow an elimination diet. This has a great impact on the

daily life of children and their parents (5–7). This stresses the need for reliable diagnostic tools. The diagnostics of hazelnut allergy consist of a careful taken history and determination of the (level of) sensitization, followed by a food challenge, ideally the double-blind placebo-controlled food challenge (DBPCFC). If a challenge is not available, the diagnosis is often based on sensitization only. Several studies have determined the role of the level of sIgE and/or the size of the SPT in relation to the risk of an allergic reaction with varying results. An IgE level ≥ 15 kU_A/l was reported to give a 95% chance of having a suggestive history of tree nut allergy (8). However, this could not be confirmed in a population exclusively suspected of hazelnut allergy (9). An SPT wheal size

Abbreviations

AUC, area under the curve; DBPCFC, double-blind placebo-controlled food challenge; ImmunoCAP, ImmunoCAP FEIA (fluor enzyme immunoassay); IQR, interquartile range; NPV, negative predictive value; PPV, positive predictive value; rCor a 1, recombinant *Corylus avellana* 1; ROC curve, receiver operating characteristic curve; sIgE, specific IgE; SPT, skin prick test.

≥ 8 mm diameter has been shown to predict a positive (mainly open) hazelnut challenge in 95% of the children (10).

To improve the performance of the ImmunoCAP to detect IgE to hazelnut extract (in birch pollen-related hazelnut allergy), the ImmunoCAP for hazelnut was enriched with recombinant Cor a 1 (rCor a 1) in 2007 (further referred to as spiking). However, two studies have shown that rCor a 1 spiking can lead to problems in distinguishing between sensitization to hazelnut and birch pollen (11,12). Furthermore, a DBPCFC is performed sporadically in previous diagnostic studies for hazelnut allergy, and a distinction between hazelnut allergy in children and adults is often not made, although children more frequently suffer from severe symptoms (2), whereas adults often suffer from mild symptoms (13).

The aim of this retrospective study was to determine the diagnostic value of the level of sIgE, the influence of rCor a 1 spiking and the size of the SPT to diagnose DBPCFC-confirmed hazelnut allergy in children. These analyses were also related to the severity of the hazelnut allergy. Other determinants such as accidental ingestion leading to an allergic reaction to hazelnut, the presence of asthma, rhinoconjunctivitis and atopic dermatitis were analyzed in relation to a hazelnut allergy.

Methods

Patient selection, sIgE, and SPT

Children who underwent a DBPCFC for hazelnut in the Center for Paediatric Allergology in Utrecht (the Netherlands) were selected for this study. The indication for a DBPCFC for hazelnut was based on a history suggestive for hazelnut allergy, or a positive sensitization for hazelnut by sIgE and/or SPT, while previous ingestion of hazelnut was unknown. Specific IgE for hazelnut, and birch pollen, was determined by ImmunoCAP (Phadia, Uppsala, Sweden). A value ≥ 0.35 kU_A/l was considered positive. Skin prick test (SPT) was performed with commercial hazelnut extract supplied by ALK-ABELLO (Nieuwegein, The Netherlands). Hazelnut extract, histamine 1% as positive control and saline as negative control were pricked into the skin of the upper back or volar aspect of the forearm. The maximum diameter of the weal size was determined and considered positive if ≥ 3 mm in the context of a positive histamine control and a negative reaction to the negative control (14).

Data with respect to accidental ingestions leading to an allergic reaction to hazelnut and the presence of other atopic features were collected from the clinical treatment chart.

Double-blind placebo-controlled food challenge

The diagnosis of hazelnut allergy was based on the DBPCFC. The DBPCFC was performed in a standardized way (2). The challenge was discontinued if objective symptoms occurred (Table 1). Suggestive subjective symptoms resulted in a positive assessment of the challenge. In three children, the DBPCFC was prematurely discontinued after the occurrence of three times oral allergy symptoms. The

severity of the hazelnut allergy was based on the outcome of the DBPCFC. The severity was classified in three ways: subjective and objective symptoms (Table 1), per organ system (Mueller) (15), and severity per organ system (Sampson) (16).

Data analysis

Specific IgE levels were compared before and after spiking, and in patients with a positive and negative DBPCFC using the Mann–Whitney *U*-test. The diagnostic value of the sIgE and the SPT for the presence of hazelnut allergy was determined by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve for all patients, and before and after spiking. The positive predictive value and negative predictive value (PPV and NPV) were determined for different cutoff points of level of sIgE and size of the SPT. Levels of sIgE and sizes of SPT were compared between patients with a hazelnut allergy with subjective and objective symptoms (using the Mann–Whitney *U*-test), and between different grades according to Sampson using the Kruskal–Wallis test. The relation between a history of accidental ingestion leading to an allergic reaction to hazelnut and presence of hazelnut allergy was assessed by chi square. The presence of other atopic features in relation to a hazelnut allergy and sIgE levels was assessed by chi-square and Mann–Whitney *U*-tests, respectively. All analyses were performed with SPSS (Version 15.0, SPSS Inc., Chicago, IL, USA).

Results

Patients

A total of 172 children underwent a DBPCFC for hazelnut between June 2004 and July 2010. One child was excluded owing to an inconclusive DBPCFC and 20 children were excluded, because it was unclear whether the level of sIgE was determined before or after spiking. Therefore, data of 151 children were analyzed. The DBPCFC confirmed a hazelnut allergy in 51 children (34%): 19 with subjective and 32 with objective symptoms. Table 2 presents the characteristics of the patients. Skin prick test for hazelnut and sIgE for birch pollen was not performed in all children (Table 2). Patient characteristics in these subgroups did not differ from the total patient group (not shown).

Table 1 Grading of the severity of the hazelnut allergy according to the symptoms occurred during the double-blind placebo-controlled food challenge

Subjective symptoms	Objective symptoms
Oral allergy	Urticaria generalized
Nausea	Angioedema
Abdominal discomfort	Emesis
Throat tightness	Diarrhea
	Rhinoconjunctivitis
	Hoarseness
	Stridor
	Wheezing

Table 2 Patient characteristics

Groups	All		Before spiking		After spiking	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Number of patients	151		60		91	
Gender, male	104	69	40	67	64	70
Age, median (IQR)	6 (5–9)		6 (5–10)		6 (5–8)	
Asthma	79	52	34	57	45	50
Allergic rhinoconjunctivitis	55	37	20	34	35	39
Atopic dermatitis	131	87	54	90	77	85
Accidental ingestion	39	26	10	17	29	32
sIgE birch pollen > 0.35 kU _A /l*	87	58	34	57	53	58
sIgE hazelnut > 0.35 kU _A /l	129	85	49	82	80	88
SPT positive ≥ 3 mm†	43	74	5	83	38	73
Double-blind placebo-controlled food challenge positive	51	34	21	35	30	33

IQR, Interquartile range; sIgE, specific IgE; SPT, skin prick test.

*sIgE birch pollen determined in 113 children, 46 before and 67 after spiking.

†SPT performed in 58 children, 6 before and 52 after spiking.

Level of sIgE for hazelnut and influence of rCor a 1 spiking

The spiking increased the level of sIgE for hazelnut significantly (median 3.3 kU_A/l vs 8.5 kU_A/l, $P = 0.019$). Level of sIgE for hazelnut was significantly higher in the children with a hazelnut allergy than in children without a hazelnut allergy (median 26.7 kU_A/l vs 2.6 kU_A/l, $P < 0.001$). The area under the curve (AUC) of the ROC curve was 0.73 (95% CI, 0.65–0.81) when considering all 151 children. Before spiking, the performance of sIgE was lower with an AUC of 0.70 (95% CI, 0.57–0.84) compared to after spiking, with an AUC of 0.75 (95% CI, 0.65–0.85). The PPV and NPV for IgE cutoff values are shown in Table 3. The maximum reached PPV before rCor a 1 spiking was 73% for a cutoff level of 26 kU_A/l; after spiking, the maximum PPV was 64% for a cutoff level of 31 kU_A/l (Fig. 1A). The spiking increased the NPV from 91% to 100% for a cutoff level of 0.35 kU_A/l (Table 3B, Fig. 1B). This NPV of 100% accounted for 12% of the children suspected of hazelnut allergy (Table 3B).

Predictive value of the size of skin prick test (SPT)

Skin prick test, performed in 52 children, was a better predictor for hazelnut allergy than the level of sIgE, with an AUC

of 0.87 (95% CI, 0.76–0.98), compared with an AUC of 0.77 (95% CI, 0.65–0.90) for level of sIgE in this same population of 52 children. The PPV and NPV for different SPT cutoff sizes are shown in Table 3A,B.

Effect of combination of level of sIgE with size of the SPT on predictive value

By combining level of sIgE after spiking with size of the SPT, the PPV reached 100% if level of sIgE for hazelnut was ≥0.35 kU_A/l and size of the SPT ≥ 16 mm or if sIgE for hazelnut was ≥5 kU_A/l and size of the SPT ≥ 13mm. However, these combinations of sIgE and SPT accounted, respectively, for 10% and 13% of the children suspected of hazelnut allergy. The PPVs for (combinations of) cutoff levels of sIgE and SPT described in literature are shown in Table 3A (8,10).

Severity of hazelnut allergy

For clinical practice, it is useful to predict which children will experience severe symptoms after ingestion of hazelnut. Level of sIgE before spiking showed a trend in discrimination between subjective and objective symptoms caused by hazelnut

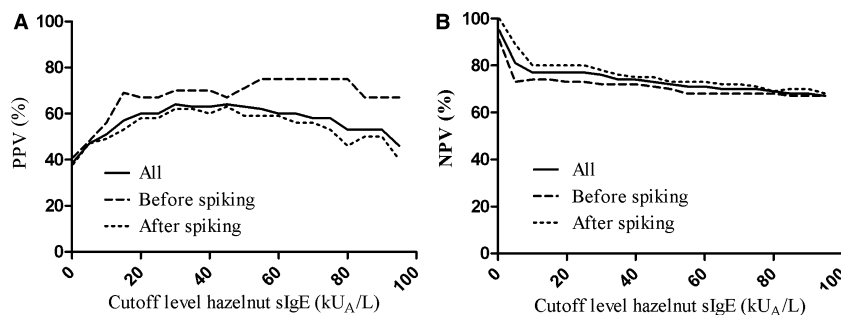


Figure 1 The PPV (A) and NPV (B) for different cutoff levels of hazelnut sIgE. Results are shown for all patients ($n=151$), and

separately for the patients before ($n=60$) and after ($n=91$) spiking.

Table 3 The positive predictive value (PPV) (A) and negative predictive value (NPV) (B) for different cutoff levels of sIgE and/or SPT and percentage of children suspected of hazelnut allergy above this cutoff level in predicting hazelnut allergy

(A)							
sIgE (kU _A /l)	SPT (mm)	PPV (%)	Percent of suspected children	PPV (%)	Percent of suspected children	PPV (%)	Percent of suspected children
		All		Before spiking		After spiking	
≥0.35		39	85	41	82	38	88
≥15		57	32	69	22	53	40
	≥3					40	81
	≥8					74	37
	≥17					100	10
≥0.35	≥3					45	73
≥0.35	≥8					74	37
≥0.35	≥17					100	10
≥15	≥3					58	23
≥15	≥8					75	15
≥15	≥17					100	2
(B)							
sIgE (kU _A /l)	SPT (mm)	NPV (%)	Percent of suspected children	NPV (%)	Percent of suspected children	NPV (%)	Percent of suspected children
		All		Before spiking		After spiking	
<0.35		95	14	91	17	100	12
<15		77	52	74	58	80	48
	<3					100	19
	<8					91	58
	<17					74	67

sIgE, specific IgE; SPT, skin prick test.

allergy ($P = 0.06$, Table 4A). In addition, level of sIgE before spiking showed a significant difference between different grades of severity according to Sampson ($P = 0.03$, Table 4B). However, both disappeared after spiking. Size of the SPT showed a significant difference between children with subjective and objective symptoms ($P = 0.02$, Table 4A) and between different grades of severity according to Sampson ($P = 0.02$, Table 4B). Level of sIgE and size of the SPT did not show a significant relation with the severity of the hazelnut allergy according to the Mueller classification (data not shown).

Other predictors: history and other atopic disease

Twenty-six percent of the children suspected of hazelnut allergy reported an accidental ingestion with allergic reaction to hazelnut in the history and resulted in a PPV of 59% for hazelnut allergy ($P < 0.001$). The prevalence of hazelnut allergy was 25% in the children that never ingested hazelnut or in which hazelnut ingestion was unclear. Asthma and rhinoconjunctivitis in the history were not predictive for a hazelnut allergy. Atopic dermatitis in the history showed a trend

($P = 0.075$) to occur more often in the children with hazelnut allergy. Children with atopic dermatitis in the history had a significantly higher level of sIgE for hazelnut compared to children without atopic dermatitis in the history (median 6.8 kU_A/l vs 1.35 kU_A/l, $P = 0.007$).

Discussion

This study showed a good NPV of diagnostic tests for hazelnut allergy in children that further improved by rCor a 1 spiking. However, the PPVs are moderate and decreased by spiking. The size of SPT was a better tool to diagnose hazelnut allergy also in combination with the level of sIgE. A history of accidental ingestion leading to allergic reaction attributed to the diagnostic work-up of hazelnut allergy in children.

The function of a sIgE test is to detect serological reactivity to a specific allergen, whereas the diagnosis of food allergy is based on clinical criteria. However, sIgE for hazelnut is often used as a diagnostic test for hazelnut allergy. Cutoff levels for hazelnut sIgE with a 95% PPV could not be determined in this study nor in a previous

Table 4 Median of the sIgE and SPT for different grades of severity of hazelnut allergy: subjective symptoms vs objective symptoms (A) and grading according to Sampson (B)

(A)										
Severity hazelnut allergy	Subjective		Objective		<i>P</i> value					
	median	<i>n</i>	median	<i>n</i>						
sIgE (kU _A /l)										
All	12	19	29	32	0.33					
Before spiking	3	9	36	12	0.06					
After spiking	56	10	25	20	0.42					
SPT (mm)										
After spiking	8	6	15	11	0.02*					
(B)										
	1		2		3		4		5	<i>P</i> value
Sampson grade	Median	<i>n</i>	Median	<i>n</i>	Median	<i>n</i>	Median	<i>n</i>		
sIgE (kU _A /l)										
All			38	21	22	6	7	7	†	0.23
Before spiking	10	17	47	10	†		14	2	†	0.03*
After spiking	1	9	33	11	22	6	7	5	†	0.84
	56	8								
SPT (mm)										
After spiking			10	5	16	4	23	3	†	0.02*
	7	5								

sIgE, specific IgE; SPT, skin prick test.

*Zero children experienced these symptoms according to Sampson during the double-blind placebo-controlled food challenge for hazelnut.

†Significant difference (*P* value < 0.05) between different ranks of severity according to Mann–Whitney *U*-test or Kruskal–Wallis test.

study on hazelnut allergy (9). Cutoff levels with a lower PPV than 90–95% have limited decisive importance (17). Specific IgE cutoff levels with 95% PPV could be established for other allergens as milk, egg, peanut, and walnut (18–20). The inability of hazelnut sIgE to reach 95% PPV might be caused by the measurement of birch pollen sIgE due to serological cross-reactivity. The effect of this serological cross-reactivity might be different between children and adults, because hazelnut allergy in children, even in a birch endemic area, may be partly pollen independent (2), in contrast to adults (12,13,21). The spiking of the ImmunoCAP for hazelnut with rCor a 1 was aimed to increase the sensitivity of the test in birch pollen-related hazelnut allergy (22), and this was shown to be at the expense of a decreased specificity (12). We evaluated the effect of spiking in two consecutive groups of children, with similar clinical characteristics (Table 2), selected before and after 2007. The spiking increased the level of sIgE for hazelnut significantly. This has already been shown before with consecutive measurements of the sIgE levels within one group of children in the USA (11). In agreement with this previous paper, we detected a strong correlation (Spearman) between level of hazelnut and birch pollen-specific IgE ($r = 0.66$, $P < 0.001$, data not shown) in children without a hazelnut

allergy, most prominently after spiking. In general, the spiking improved the performance of the sIgE as shown by the AUC. After spiking, the sIgE cutoff value of <0.35 kU_A/l is a reliable tool in the exclusion of hazelnut allergy and accounts for 12% of the children suspected of hazelnut allergy. However, the spiking resulted in a higher false positive rate for the sIgE cutoff value of <0.35 kU_A/l (62% vs 59%), both higher than the 40% published for tree nuts in previous literature (8). Earlier studies showed a false negative rate of 22% for the sIgE (8,9), compared with 9% before spiking in our study. These differences might be explained by a different prevalence of hazelnut allergy or the more heterogeneous patient populations in these previous studies. Both children and adults were included (8), hazelnut allergy was not confirmed by a DBPCFC (2,4,23), and patients with a tree nut allergy were included (2).

In agreement with literature (8), our study showed that SPT was more reliable in diagnosing hazelnut allergy compared with the level of sIgE. The clinically used SPT cutoff value (<3 mm) can rule out hazelnut allergy in 19% of the children. The PPV was 100% for the SPT cutoff value ≥ 17 mm, however, accounting for 10% of the children. This suggests that the SPT might be a useful tool for a significant

proportion of the children to diagnose or exclude hazelnut allergy, especially in settings in which the DBPCFC is not, or limitedly, available. In contrast with the previously published >95% PPV for the SPT cutoff value ≥ 8 mm (4), the PPV for this cutoff value was 74% in our study. A different commercial SPT extract was used in this previous study. The composition of commercially available reagents shows variability between different batches and companies (24), hampering SPT standardization. The PPV for hazelnut allergy could be increased by combining the level of the sIgE and the size of the SPT. However, only a minority of the children suspected of hazelnut allergy will reach these cutoff levels with a high PPV.

Our study was performed in a third line referral population. It is important to realize that the prevalence of a disease influences the PPV and the NPV. Therefore, our data may represent an overestimation of the PPV and an underestimation of the NPV as compared to other settings (primary and secondary care).

sIgE levels showed a trend in discriminating between severity of hazelnut allergy on group level. The spiking resulted in a loss of this discrimination. Previous studies could not show a predictive role for level of sIgE for (hazel) nuts on the severity of the clinical reaction based on history (8,25). Size of the SPT was a good predictor for severity of the hazelnut allergy in children (on group level), comparable with a previous study (8).

Our study showed a predictive value of 59% for reported accidental ingestion of hazelnut. In peanut allergy, a history of accidental ingestion of peanut was shown to predict peanut allergy in children independent of sensitization. The severity of the previous reaction was the strongest predictor for peanut allergy in that model (26). However, the severity of the symptoms after accidental ingestion was not a predictor for hazelnut allergy in our study (data not shown). Additionally, atopic dermatitis had a higher prevalence in children with hazelnut allergy. Eczema (early onset) has been shown to be a risk factor for peanut allergy in children (27,28).

In conclusion, this study showed that the NPV of diagnostic tests for hazelnut allergy in children is good and further improved by rCor a 1 spiking. However, the PPVs are moderate and decreased by spiking. The SPT might reduce the amount of necessary DBPCFCs. This shows that until better tools have been developed, such as component-resolved diagnosis, the DBPCFC remains the mainstay of the diagnostics of hazelnut allergy in children, to correctly diagnose hazelnut allergy and prevent unnecessary elimination diets.

Author contributions

L.J. Masthoff substantially contributed to design, concept, acquisition of data, analysis and interpretation of data, drafting the article and final approval of version to be published. S.G. Pasmans and E. van Hoffen substantially contributed to design, interpretation of data, revising critically for important intellectual content and final approval of version to be published. M. Knol substantially contributed to design, conception, analysis and interpretation of data, revising critically for important intellectual content and final approval of version to be published. C.A. Bruijnzeel-Koomen and A.C. Knulst substantially contributed to interpretation of data, revising critically for important intellectual content and final approval of version to be published. A.E. Flinterman and P. Kentie substantially contributed to acquisition of data, revising critically for important intellectual content and final approval of version to be published. Y. Meijer substantially contributed to design, concept, interpretation of data, revising critically for important intellectual content and final approval of version to be published.

Conflict of interest

On behalf of all authors (L.J. Masthoff, S.G. Pasmans, E. van Hoffen, M.J. Knol, C.A. Bruijnzeel-Koomen, A.E. Flinterman, P. Kentie, A.C. Knulst, Y. Meijer), I declare that none of the authors has to disclose any potential conflict of interest.

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