

Low-Dose Oral Food Challenge with Hazelnut: Efficacy and Tolerability in Children

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Keywords

Children · Hazelnut · Low-dose oral food challenge

Abstract

Background: Hazelnut allergy (HA) is one of the more common food allergies (FAs) in Europe with a prevalence of 0.2%. The gold standard for diagnosing FA is oral food challenge (OFC) with the culprit food. Another purpose of OFC is to identify the "threshold level" of food as the dose that elicits symptoms. In this way it is possible to avoid a strict elimination diet and to determine the minimal quantity of the culprit food tolerated by the patient. **Objective:** The aim of our study was to assess the efficacy and tolerability of hazelnut low-dose OFC (H-LDOFC) in children with HA. **Methods:** From January 2015 to December 2016, we retrospectively analyzed the charts of patients referred to Allergy Unit of Meyer Children's Hospital, Florence, Italy for a history of HA. Prick by prick (PbP) and specific serum IgE (s-IgE) to hazelnut were performed. We proposed conducting an H-LDOFC to parents of children with HA. The H-LDOFC was considered completed when a cumulative dose of 2.5 g of hazelnut was reached. We divided the patients who underwent the H-LDOFC into an asymptomatic and a symptomatic group. For statistics we used SPSS for Windows version 16.0 and

conducted a *t* test for comparing the averages, considering a *p* value of <0.05 significant. **Results:** Forty-three out of 70 patients (61.4%) with HA underwent an H-LDOFC. The PbP to hazelnut (mean ± SD) was 7.2 ± 2.9 mm and the s-IgE to hazelnut 25.3 ± 32.5 kU/L. Twenty-eight out of the 43 patients (65.1%) who underwent H-LDOFC reached the cumulative dose of 2.5 g of hazelnut. During the H-LDOFC, 20/43 patients (46.5%) had no reactions and 23/43 patients had a total of 55 reactions: 34 (61.8%) oral allergy syndrome, 8 (14.5%) rash, 6 (10.9%) abdominal pain, 2 (3.6%) urticaria, 2 (3.6%) angioedema, and 3 (5.4%) dyspnea. Atopic dermatitis was found to present the only statistically significant difference (*p* = 0.002) in patients with symptoms compared to asymptomatic patients during H-LDOFC. **Conclusions:** To our knowledge, this was the first study to assess the efficacy and tolerability of H-LDOFC in a pediatric population. Our study suggests that in children with HA, H-LDOFC is well accepted and safe because adverse reactions are mild and the majority are represented by localized symptoms (oral allergy syndrome) and efficient, especially in terms of improvement of quality of life. For these reasons it could be more extensively used in the treatment of HA.

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Introduction

Hazelnut allergy (HA) is one of the more common food allergies (FAs) in Europe with a prevalence of 0.2% [1]. In Europe and Italy, hazelnut (*Corylus avellana*) is the main cause of anaphylaxis in children aged 2–6 years [2].

The gold standard to diagnose FA is the oral food challenge (OFC) with the culprit food. However, this procedure is not free from the risk of possible reactions, even severe, such as anaphylaxis [3]. Another purpose of the OFC is to identify the “threshold level” of food as the dose that elicits symptoms. In this way it is possible to avoid a strict elimination diet and to determine the minimal quantity of the culprit food tolerated by the patient [4].

Recently, a stepwise OFC with milk, egg, wheat, and peanut was reported to be useful and effective in improving the quality of life of children with FAs. The stepwise OFC, which consists in starting with a low dose and progressing to medium and full doses, is an effective approach to enable children with FAs to determine the maximum quantity of the allergen that they can safely consume [5].

The first aim of our study is to assess the efficacy and tolerability of hazelnut low-dose OFC (H-LDOFC) in children with HA. The second aim was to assess the compliance to H-LDOFC after 1 year through a phone call interview.

Methods

From January 2015 to December 2016, we retrospectively analyzed the charts of patients referred to the Allergy Unit of Meyer Children's Hospital, Florence, Italy for a history of tree nut allergy, in particular to hazelnut. Prick by prick (PbP) hazelnut and skin prick tests to dust mite, birch, *C. avellana*, and grass were performed using commercial extracts at 0.1 mg/mL from ALK-Abellò, Milan, Italy. The positive and negative controls for the skin prick test were obtained using histamine (10 mg/mL, ALK-Abellò) and normal saline, respectively. A wheal size equal to or larger than the wheal obtained with histamine, 15 min after testing, was considered positive.

In patients with PbP positive to hazelnut, specific serum IgE (s-IgE) to hazelnut and Cor a 1, Cor a 8, Cor a 9, and Cor a 14 (ImmunoCap RAST, Uppsala, Sweden) were performed. Levels >0.10 kU/L were considered positive. We proposed to parents of children with HA to have H-LDOFC done, and those who accepted signed an informed consent form.

The H-LDOFC protocol consisted of a hospital stay of two consecutive days every 3 months. On the first day, the child was given increasing doses of hazelnut starting, from an initial dose of 5 mg (0.00075 g of hazelnut protein) and increasing the dose every 30 min according to the following scheme: 5 + 10 + 25 + 50 + 100 + 150 + 300 + 600 + 1,200 mg. The H-LDOFC was considered

completed when the child reached a cumulative dose of 2,500 mg of hazelnut (0.375 g of hazelnut protein) without presenting reactions. The OFC was considered positive if any objective skin, respiratory and/or cardiovascular, neurologic, or gastrointestinal symptoms were observed. Patients were observed for 2 h after the last hazelnut dose intake if they had a negative outcome and 2 h after the resolution of symptoms for any reaction. If the OFC was positive on the first day, the child was discharged and advised to take the hazelnut at home three times a week with a dose equal to the maximum dose tolerated during hospital stay, until the next hospital stay. If the OFC was negative on the first day, on the second day the child was given the dose after the one reached the day before and incremental doses every 30 min. If the OFC was negative, the child completed the H-LDOFC and continued to take the hazelnut at home three times a week as maintenance dose.

We evaluated the number of children who had discontinued, finished, or were still in the process of H-LDOFC. We divided the patients who underwent H-LDOFC into asymptomatic and symptomatic patients. We evaluated between these two groups whether there were any statistically significant differences in terms of history of allergic oculorhinitis, allergic asthma, atopic dermatitis, FAs, symptoms presented at first reaction to hazelnut, skin test values, and s-IgE to hazelnut.

A follow-up interview by phone was performed 1 year after the achievement of 2,500 mg of hazelnut to know whether the patients were still assuming hazelnut, at which dose, how frequently, and whether any adverse reactions had occurred.

For statistics we used SPSS for Windows version 16.0. We did a *t* test for comparing the averages. We considered a *p* value <0.05 to be significant.

Results

Forty-three out of 70 patients (61.4%) (27 males [62.8%] and 16 females [37.2%], mean age 10 years [range 5–16 years]) with HA underwent H-LDOFC. Twenty-nine out of 43 patients (67.4%) presented symptoms involving a single organ; 14/43 patients (32.5%) presented anaphylaxis (13 patients [92.8%] mild anaphylaxis, 1 patient [7.2%] moderate anaphylaxis, and none severe anaphylaxis).

The 43 patients who underwent the H-LDOFC presented (mean ± SD): PbP to hazelnut 7.20 ± 2.98 and s-IgE to hazelnut 25.37 ± 32.44 kU/L. The research of H molecular allergens s-IgE was performed in 23 out of 43 patients (53.5%), and the average value was 7.70 ± 11.70 kU/L for Cor a 1, 2.10 ± 8.40 kU/L for Cor a 8, 20.50 ± 35.36 kU/L for Cor a 9, and 5.60 ± 31.90 kU/L for Cor a 4.

Twenty-eight out of 43 patients (65.1%) who underwent H-LDOFC reached the cumulative dose of 2.5 g; 15/43 patients (34.8%) are still ongoing and they succeeded in tolerating a mean dose of 254.6 ± 233.29 mg of hazelnut. The average time to complete the H-LDOFC was 5 months (range 3–12 months).

Table 1. Comparison between symptomatic and asymptomatic patients during H-LDOFC

	Symptomatic patients	Asymptomatic patients	<i>p</i> value
Allergic oculorhinitis	8/23 (34.8%)	2/20 (10%)	ns
Allergic asthma	6/23 (26.0%)	3/20 (15%)	ns
Atopic dermatitis	14/23 (60.9%)	2/20 (10%)	0.002
Allergy to other tree nuts	20/23 (87.0%)	16/20 (80%)	ns
Other food allergy	15/23 (65.2%)	12/20 (60%)	ns
Symptoms at first reaction to hazelnut			
Cutaneous symptoms	7/23 (30.4%)	7/20 (35%)	ns
Respiratory symptoms	2/23 (8.7%)	3/20 (15%)	ns
Gastrointestinal symptoms	8/23 (34.8%)	3/20 (15%)	ns
Anaphylaxis	6/23 (26.1%)	7/20 (35%)	ns
Dust mite allergy	13/20 (65%)	10/17 (58.8%)	ns
Grass allergy	12/17 (70.6%)	9/17 (52.9%)	ns
Birch allergy	13/15 (86.6%)	6/16 (37.5%)	ns
<i>Corylus avellana</i> allergy	2/17 (11.8%)	2/7 (28.6%)	ns

Values are presented as number of patients (%). H-LDOFC, hazelnut low-dose oral food challenge; ns, not significant.

During the H-LDOFC, 20/43 patients (46.5%) did not present any reactions; 23/43 patients (53.5%) presented a total of 55 reactions: 34 (61.8%) oral allergy syndrome, 8 (14.5%) rash, 6 (10.9%) abdominal pain, 2 (3.6%) urticaria, 2 (3.6%) angioedema, and 3 (5.4%) dyspnea.

Atopic dermatitis was found to present the only statistically significant difference in patients with symptoms during H-LDOFC compared to asymptomatic patients ($p = 0.002$) (Tables 1, 2).

At 1-year follow-up, all patients who had completed H-LDOFC continued to consume hazelnut, or products containing it, at a dose not higher than 2,500 mg at least once a week, without any adverse reactions.

Discussion

To our knowledge, this was the first study to assess the efficacy, tolerability, and usefulness of H-LDOFC in a pediatric population. In a previous study [6], a very-low-dose oral immunotherapy with hazelnut (maximum dose 13 mg) was reported to be safe and efficient, with an increase of five times the tolerated dose after 8–12 weeks of treatment. In our study, the maximum quantity of hazelnut that children could safely consume was much higher (2.5 g) and compliance was very good. Skin prick test and s-IgE values were found to be predictive of HA [7, 8]. Our patients had relatively high values of skin prick test (7.2 ±

Table 2. Comparison between symptomatic and asymptomatic patients during H-LDOFC in terms of allergy testing

	Symptomatic patients	Asymptomatic patients	<i>p</i> value
PbP hazelnut, mm	8.91±2.81	5.25±1.74	ns
s-IgE hazelnut, kU/L	31.12±36.99	18.76±25.61	ns
s-IgE Cor a 1, kU/L	6.04±11.14	9.85±11.74	ns
s-IgE Cor a 8, kU/L	0.48±1.18	6.08±15.35	ns
s-IgE Cor a 9, kU/L	18.30±31.88	17.47±40.44	ns
s-IgE per Cor a 14, kU/L	16.06±30.75	3.27±4.59	ns

Values are presented as mean ± SD. H-LDOFC, hazelnut low-dose oral food challenge; ns, not significant; PbP, prick by prick; s-IgE, specific IgE.

2.98 mm) and s-IgE to hazelnut (25.4 ± 32.4 kU/L) and underwent H-LDOFC with a good success rate (66% of patients completed it) and with mild and local adverse reactions (oral allergy syndrome, abdominal pain, rash). Children with atopic dermatitis in their history had significantly higher levels of s-IgE for hazelnut compared to children without atopic dermatitis, as has been already reported [9]. In our study, the presence of atopic dermatitis in the history was statistically significantly different in patients with symptoms during H-LDOFC compared to asymptomatic patients. Atopic dermatitis is a well-

known risk factor to the development of FA; in fact the presence of epidermal barrier dysfunction allows increased exposure to food allergen through the skin, leading to sensitization [9] and, therefore, to clinical FA [10]. Cor a 14 was found to be a marker of HA [8]. In our study, even though Cor a 14 values in symptomatic patients were higher than in asymptomatic patients, not statistically significant differences were found, as was the case for the other molecules studied, probably due to the fact that we performed that measurement in a minor proportion of patients.

In conclusion, our study suggests that in children with HA, the H-LDOFC is well accepted and safe because the adverse reactions are mild and the majority are represented by localized symptoms (oral allergy syndrome) and the procedure is efficient, especially in terms of improvement of quality of life. For these reasons, it could be more extensively used in the treatment of HA.

Statement of Ethics

The patients' parents gave their written informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

S. Barni made substantial contributions to the conception and design of the paper and was involved in the drafting of the manuscript. F. Mori and E. Novembre critically revised the paper and gave the final approval of the version to be published. A. Piccorosi, L. Sarti, M. Maresca, G. Liccioli, and M. Giovannini made substantial contributions to data acquisition. N. Pucci made substantial contributions to the conception and design of the paper.

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