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Research Article

HAZELNUT ALLERGY IN THE ALBANIAN POPULATION IN JULY-DECEMBER 2023 (Case study)

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Abstract:
Introduction: Hazelnut is a common cause of systemic food-induced allergic reactions and anaphylaxis in Europe, especially in young children. The purpose of this study is to identify the frequency of cases of allergy caused by hazelnuts in the Albanian population in the period July-December 2023.
Materials and methods: 353 people of different age groups from the entire Albanian Republic participated in this study. A venous blood sample was taken from each person to perform the specific IgE test for food allergens using the Polycheck reagent with 30 total allergens.
Results and discussions: from the results of the laboratory tests it following:

- In July, there were a total of 61 patients, of which 12 (20%) were IgE+ for the hazelnut allergen.
- In August, there were 61 patients, of which 22 (36%) were IgE+ for the hazelnut allergen.
- In September, there were a total of 50 patients, of which 7 (14%) were IgE+ for the hazelnut.
- In October, there were 57 patients, of which 5 (8.8%) were IgE+ for the hazelnut allergen.
- In November, out of 51 total tests, 9 or (17.6%) of them resulted IgE+ for the hazelnut allergen.
- In December, out of 73 total tests, 13 (17.8%) resulted IgE+.

Conclusions: Hazelnut allergy is more pronounced in the summer season in our country (27.8%). The month with the highest prevalence of hazelnut allergy is August.

Keywords: Allergic Reaction, IgE +, Hazelnut, Month.

I. INTRODUCTION

The tree that produces hazelnuts is the common hazel, *Corylus avellana*, which is part of the birch family. Hazelnut is a common cause of systemic food-induced allergic reactions and anaphylaxis in Europe, especially in young children [1,2]. Hazelnut allergy can manifest itself in different ways depending on the individual's sensitization. Individuals who are primarily sensitized to seasonal pollens may experience mild oropharyngeal symptoms when consuming hazelnuts, which is called oral allergy syndrome (OAS).

Ten hazelnut allergens have been identified and biochemically classified and named Cor a 1, Cor a 2, Cor a 8, Cor a 9, Cor a 10, Cor a 11, Cor a 12, Cor a 13, Cor a 14 and Cor a thaumatin-like protein (TLP)

Cor a 1 sensitization is associated with clinical hypersensitivity reactions that are usually local and mild [8]. Toasted or boiled hazelnuts are usually tolerated. Cor a 1 sIgE has low PPV, NPV, (Regarding negative. positive predictive value (NPV) sensitivity and specificity and is a poor discriminator for primary hazelnut allergy [3,4]. Children may develop Cor a1 sIgE as a result of interaction with PR-10 from birch or birch tree pollen This is the main sensitizer [6,5].

Cor 2 is also associated with cross-reactivity with birch and many other plant pollens [10], however, further studies are needed to clarify its clinical relevance.

Cor a 8 can be associated with systemic reactions and cross-reactions with LTPs of other plants [7]. There is an association between IgE to Cor a 8 and IgE to LTP in other foods, especially nuts [6,8].

Cor a 9 is an 11S globulin and Cor a 14 is a 2S albumin. They have a very weak correlation with sIgE to pollen, in contrast to Cor a 1 and Cor a 2 [10]. Cor a 9 has significant homology to proteins found in peanut and soybean [9]. SIgE for Cor a 9 and Cor a 14 are the most accurate components for a primary diagnosis of hazelnut allergy and they are associated with a high risk of systemic reactions [6,4,10–14].

Cor a 14 appears to have even better diagnostic accuracy than Cor a 9 in predicting risk for moderate-severe reactions to hazelnuts [21,22,3,4]. In general, the NPVs of Cor a9 sIgE and Cor a 14 sIgE are high [64]. Combined IgE testing for Cor a 9 and Cor a 14 has shown a good NPV (>90%) for primary hazelnut allergy [4]. On the other hand, the PPVs of Cor a 9 sIgE and Cor a 14 sIgE are low [3].

Cor a 10 is a heat shock protein. Cor a 11 is a 7S globulin.

Oleosins are a group of proteins that have been identified in various nuts. In hazelnuts, the known oleosins are Cor a 12 and Cor a 13, with unclear clinical significance [62]. A new hazelnut oleosin called Cor a 15 has recently been identified as a possible cause of reactions to hazelnuts in a subset of pediatric patients [23]

Sensitization to hazelnuts is common in adults, especially in birch endemic areas where cross-reactivity between birch PR-10 (Bet v 1) and hazelnut PR-10 (Cor a 1) proteins In central and northern Europe, Cor a 1 IgE is detected in 60-90% of individuals with hazelnut sensitization [6]. Cross-sensitivity is usually associated with mild OAS (itching and swelling of the tongue and lips).

In school-age children living in the Mediterranean area, OAS is associated with sensitization to LTPs and PR-10 [15]. In younger children, the role of birch pollen cross-reactivity is of secondary importance, while primary sensitization to SSPs, i.e., Cor a 9 and Cor a 14, and LTPs, i.e., Cor a 8, is more common [6,16]; the latter is particularly true in the Mediterranean area, with a prevalence ranging from 36 to 83% [6,17]. An American study [16] also showed that children under three years of age are mainly sensitized to SSPs, while sensitization to cross-reactive Cora 1 is much more common in adults than in children.

II. MATERIAL AND METHOD

For the realization of this study, an experimental study was carried out.

Sample collection

353 people were involved in the realization of this study. Some of them were asymptomatic and some others manifested different clinical signs that referred to illogical reactions. The age groups taken in the study were from 6 months to 78 years. A 5ml venous blood sample was taken from each of them with a butterfly vacuum system and tested for Specific IgE antibodies. Blood was collected from forearm veins using a 21G vacuum system. All samples were identified and homogenized at least five times. Each sample was allowed to set for 30 minutes at 18–25ºC. All tubes were centrifuged at 1500g/3500RPM for 10 minutes at 18 -25 C.

All samples were checked for hemolysis and lipemia.

Analyzing the sample

The measurement of specific IgE was performed with the Indirect ELISA method using Policheck LOT 18 REF.WB05 reagents. The analysis of the tests was carried out according to the laboratory protocols

related to pre-analytical, analytical and post-analytical phases. The laboratory tests were carried out in the Genius Shpk laboratory.

Reagents in use were stored at 2–8 °C and protected from contamination.

Features of the analysis

→ Sample material: Serum

→ Analysis duration: Manual procedure: 2.5 hours,

→ Lower limit of detection: 0.15 kU/l

→ Specification: human IgE; no cross-reaction with IgG, IgA, IgD, IgM

Necessary materials

→ IT equipment: Personal computer (Windows 7 or higher versions, Net Framework 3.5), printer, flat-bed scanner (search for recommended models or check at www.polycheck.de)

→ Biocheck Imaging Software (BIS): for analysis, calculations and reports

→ Laboratory equipment: Oscillating shaker (30 rpm), pipette 200 -1000µl; Multipete (1ml) to dispense the WASH solution

→ Demineralized water for the preparation of WASH solution

Test Method and Principle

The Polycheck® Screening Assay is an immunoassay for the quantitative measurement of allergen-specific IgE in serum. The respective allergens are coated separately on the strips as well as the calibrator in a holder which is fixed in the well of the Polycheck® cassette. During incubation of the patient's serum, allergen-specific IgE binds to the respective allergens.

Unbound serum components are removed by washing. Anti-IgE antibodies labeled with monoclonal ligands bind to allergen-bound IgE. Unbound antibodies are removed by washing. Enzyme-tagged anti-ligands bind to immune complexes; excess enzyme conjugate is removed by washing.

The substrate solution is added and specially bound enzymes convert the colorless substrate into a dark precipitate. The color intensity of the lines is proportional to the corresponding concentration of allergen-specific IgE in the patient's serum.

With the help of Biocheck Imaging Software (BIS) and a computer, Polycheck® cassettes are interpreted. Each single allergen will be identified and, according to the calibrator curve present in each cassette, the concentration of each specific allergen IgE is quantified.

Test Performance

! All test components should be at room temperature and mixed well.

! Use only the reagent parts supplied with the current kit.

! Powder wash buffer should be diluted with demineralized water at least 30 minutes before use.

Avoids foaming.

! Test cassette membranes should not be allowed to dry during analysis.

! All incubation steps are performed at room temperature (18 – 24 °C) and with continuous shaking.

! For the correct interpretation of the test results, a flatbed scanner with a CCD sensor and a scanning resolution of 600 DPI should be used.

Test steps

The Policheck kit contains 24 ready-to-use cassettes. Cassettes are stored at 2-8 degrees Celsius before use.

1. Identification of Polycheck® allergy tapes only on the long side of the tape.

2. Moisten the cassettes with 1 ml of wash solution, and remove the wash buffer by tapping upside down on absorbent paper.

3. Add to the allergy cassettes with 250 µl of initial solution Polycheck® Start solution, which is a buffer with protein content. (blue cap) and incubate for 60 seconds (always pipet into the gap). Carefully tap the cassettes upside down on absorbent paper.

4. Add 200 µl of the respective patient's serum to the cassette and incubate for 60 minutes on a shaker.

Place the MTP holder in the middle of the shaker. The orientation of the MTP holder on the shaker must remain the same throughout the test procedure.

5. Rinse three times with 1 ml Polycheck® wash solution. Tap the cassettes carefully upside down on absorbent paper. Add 250 µl wash buffer and incubate for 5 minutes on a shaker.

6. Repeat step 5. Decant and tap the cassettes carefully.

7. Pipette 250 µl of Polycheck® anti-IgE antibody (green cap) and incubate for 45 minutes on a shaker. Rinse three times with 1 ml wash buffer. Tap the cassettes carefully on absorbent paper.

8. Add 250 µl of enzyme-labeled anti-ligand Polycheck® (white cap) and incubate for 20 minutes on a shaker. Decant and wash as described in 7. Tap cassettes carefully on absorbent paper.

9. Pipette 250 µl of Polycheck® substrate solution (black cap) and incubate for 20 minutes in the dark. Decant and wash as described in 7.

10. Dry the membrane and evaluate the Polycheck® allergy cassettes using a scanner and the Biocheck imaging software

III. RESULTS

The data of this study includes the period July- December 2023. In total, there are 353 samples analyzed in the laboratory.

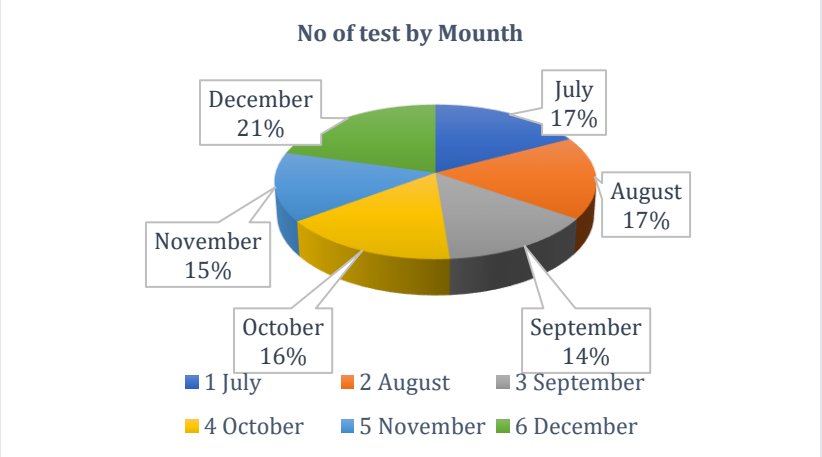
Table 1. Table 1 shows the distribution by month (July-December) of the number of specific IgE tests. There is an increase in the number of tests in December

Distribution of tests by month

No.	Month	No. of tests by month	Total in %
1	July	61	17.28
2	August	61	17.28
3	September	50	14.16
4	October	57	16.15
5	November	51	14.45
6	December	73	20.68
Total		353	100.00

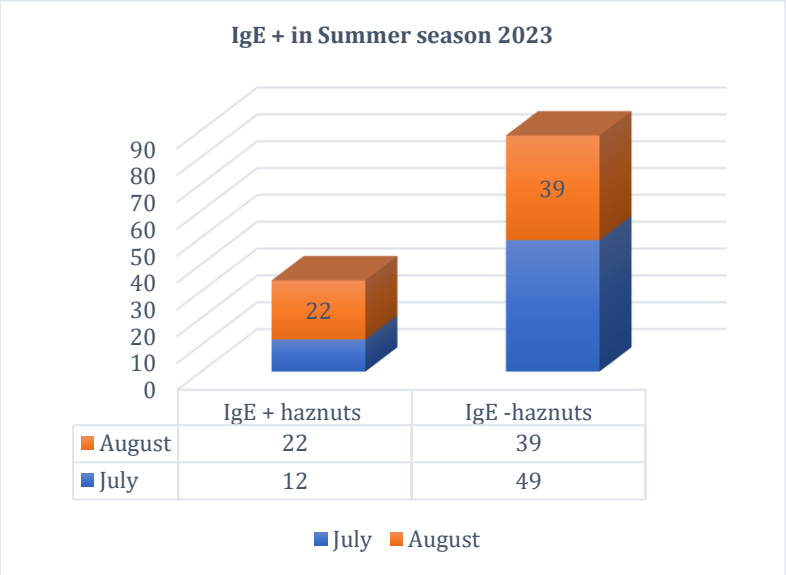
They are followed by the graphic presentation, that shows the distribution in the percentage of tests performed during different months.

Graph 1. This graph shows the distribution in % of tests by month. From the graph, the highest % in several tests belongs to December (21%).

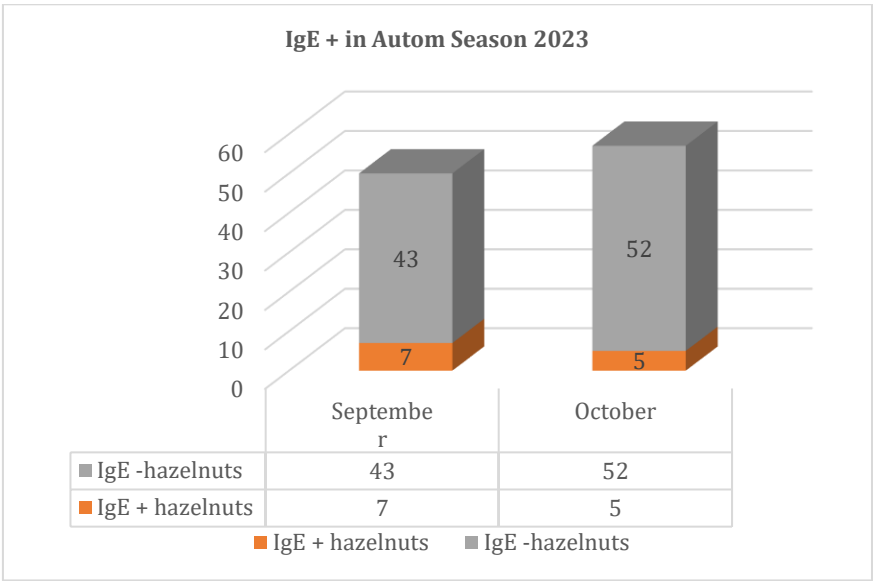


To identify the biggest number of cases of this allergy, the study area was divided by season.

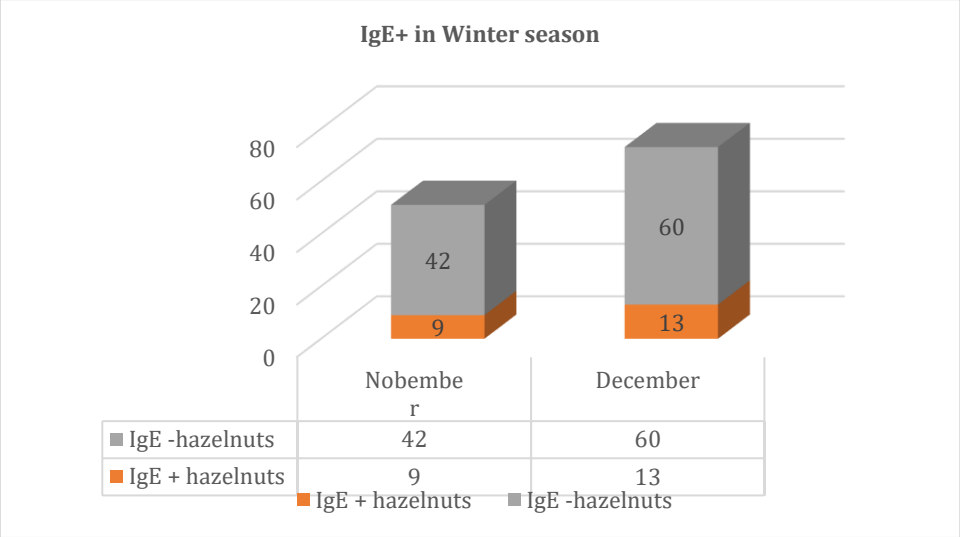
Graph 2. In this graph, IgE+ from hazelnuts is presented for July - August 2023. In July, there were a total of 61 patients, of which 12 (20%) were IgE+ for the hazelnut allergen. In August, there were 61 patients, of which 22 (36%) were IgE+ for the hazelnut allergen. Total positive tests 27.8% in the summer season.



Graph 3. In this graph, IgE+ is shown for the period September-October 2023. In September, there are a total of 50 patients, of which 7 (14%) were IgE+ for the hazelnut allergen. In October, there were 57 patients, of which 5 (8.8%) were IgE+ for the hazelnut allergen. Total positive tests 11.2% in the autumn season.



Graph 4. This graph shows IgE+ of hazelnuts for the winter season of 2023. In November, out of 51 total tests, 9 or (17.6%) of them resulted in IgE+ for the hazelnut allergen. In December, out of 73 total tests, 13 (17.8%) resulted in IgE+. Total positive tests 17.7% in the winter season.



IV. DISCUSSION

Hazelnut allergy is common, often persistent and associated with the risk of severe systemic reactions and anaphylaxis. Usually, this allergy can be primary, but it can be the result of an immune system reaction from another allergen, which can be similar from a protein structural point of view. Their diagnosis is important because of the risk of severe allergic reactions such as anaphylactic shock. Diagnosis of allergy cases requires cross-checking the patient's clinical data with skin tests or blood tests such as specific IgE. It is important to emphasize the role of laboratory tests in diagnosis with the aim of early identification to avoid accidental contact with these allergens.

In this study, a high number of patients manifested hazelnut allergies in the summer season. This conclusion can be related to the consumption of hazelnuts as fresh, unprocessed fruit due to the high temperatures, allowing the proteins to be allergens. strong.

Since they are a food with dense energy and high nutritional value, they are used to balance the diet, thus helping to reduce the risk of cardiovascular problems and type 2 diabetes. This is related to increasing the awareness of the population for the consumption of products of plant origin.

Another element that should be mentioned is the fact of individual sensitization since hazelnut allergy depends on the way the organism is sensitization. Individuals who are primarily sensitized to seasonal pollens may experience mild oropharyngeal symptoms when consuming hazelnuts, which is called oral allergy syndrome (OAS).

Cases of IgE + as a result of cross-reaction of this allergen with allergens similar mainly to birch pollen and walnut pollen should also be taken into account. Birch is an endemic plant for the Mediterranean and as such the degree of exposure to it is great. Tree pollen can be carried long distances by wind or even a light breeze, so you don't need to be in direct contact with birch trees to experience symptoms.

Pollen sensitivity can also cause pollen food syndrome or oral allergy syndrome. This is a hypersensitivity reaction to fruits, vegetables and nuts (often referred to as plant-based foods) that usually causes mild irritant symptoms such as an itchy mouth, lips and throat when eaten in their raw form. With food pollen syndrome, many plant-based foods—fruits, vegetables, nuts, and grains—have a protein structure that is very similar to tree pollens (this is called cross-reactivity). However, the immune system doesn't always know the difference between the pollen in the trees you inhale and the structure of the pollen in the plant-based foods you eat. With pollen food syndrome, the immune system recognizes the food protein you eat as an allergen and creates an allergic response. Consequently, cross-reactivities of serological tests do not

always correspond to actual sensitization often occur. Future developments may see a serological test using epitopes for IgE, which would thus improve the specificity of these tests.
It is worth mentioning the fact that hazelnut products are often packaged and to increase the shelf life of the product, different adjuvants and preservatives are added, thus increasing the possibility of cross-reactions. In these cases, the manifestations of allergy symptoms are not primarily caused by the allergen but by an external factor.

It is also necessary to study the immune mechanisms of action that bring about this manifestation, which may be modified or changed as a result of various genetic mutations since it is known that climate changes, radiation and the use of various chemical substances are potential risk factors for mutations. different.

V. CONCLUSION

IgE-mediated tree nut allergy has a prevalence of less than 2%, while estimates of possible tree nut allergy are 0.05–4.9% [1]. Among nuts, hazelnut is the most frequent cause of systemic hypersensitivity reactions in Europe [1,24,25-27].

Sensitization to hazelnuts is common in adults, especially in birch endemic areas where cross-reactivity between birch PR-10 (Bet v 1) and hazelnut PR-10 (Cor a 1) proteins is the driving force [6]. In Central and Northern Europe, Cor a 1 IgE is detected in 60-90% of individuals with hazelnut sensitization [6]. Cross-sensitivity is usually associated with mild OAS (itching and swelling of the tongue and lips).

In school-age children living in the Mediterranean area, OAS is associated with sensitization to LTPs and PR-10 [15]. In younger children, the role of birch pollen cross-reactivity is of secondary importance, while primary sensitization to SSPs, i.e., Cor a 9 and Cor a 14, and LTPs, i.e., Cor a 8, is more common [6,16]; the latter is particularly true in the Mediterranean area, with a prevalence ranging from 36 to 83% [6,17]. An American study [16] also showed that children under three years of age are mainly sensitized to SSPs, while sensitization to cross-reactive Cora 1 is much more common in adults than in children.
The diagnosis of hazelnut allergy [28] includes a history of clinical hypersensitivity reactions after consumption of hazelnuts, a positive hazelnut skin prick test (SPTs) response and/or detection of hazelnut-specific IgE antibodies (sIgE).

A positive finding of SPT and sIgE is not always necessary to make a diagnosis. Even when the SPT or sIgE results are negative (although rarely), it is possible that the child has an allergy.

The oral food challenge (OFC), especially the double-blind placebo-controlled food challenge (DBPCFC), is considered the gold standard for confirming the diagnosis [50].

In a similar study [19,20] of 383 adult patients in Zurich, it was found that hazelnut is the most frequent cause of IgE-mediated food allergy. The main allergen of hazelnut has been identified as a protein associated with the pathogenesis of approx. 17 kd which is homologous to the major birch allergen (Bet v 1).10 Consequently, allergy to hazelnut is particularly frequent in subjects with a respiratory allergy to birch, hazelnut, and alder pollen. Hazelnuts are widely used in prepackaged foods, especially in the production of sweets and ice cream. The widespread use of hazelnuts in the food industry poses a significant risk to subjects with a hazelnut allergy because the food label may not list foods that are present in small amounts or foods that may be found contaminated.

Also in this study, it was noticed that the patients with hazelnut allergy in Milan and Zurich were sensitized by birch pollen. These areas, as well as the Mediterranean, are endemic to birch. This could also be the reason why we have such a high number of hazelnut allergies in our country. The fact that all patients in the Copenhagen and Zurich groups were allergic to birch pollen, and had the lowest mean provocative dose of hazelnut could be explained by the higher exposure to birch pollen seen in northern European countries.

Since pollen allergies but also food allergies have an increasing prevalence, the realization of tests such as SSPs have a higher diagnostic value in predicting the risk of severe reactions [29] after co-sensitization to pollen hazelnut and birch makes primary allergy less likely [30].

In primary hazelnut allergy, reactions can be severe and anaphylaxis is not uncommon [2,31,32] These reactions can also be fatal. Physical exertion after ingestion of hazelnuts may be necessary for the development of anaphylaxis [33]. The first reaction may occur after the first known ingestion in early childhood, and in young children, severe reactions are more common [29,34]. Half of all children with nut allergy have an anaphylactic reaction as their first clinical manifestation, with no significant difference between types of nuts [18].

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