Clinical Performance of Commercial ISAC 112 Allergen Microarray Versus Noncommercial RIRAAF Platform for the Diagnosis of Plant Food and Olive Pollen Allergies

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The combination of molecular biology and technological advances in recent years has enabled the development of new methods for the determination of serum specific IgE (sIgE) [1] to different allergens using a single determination method with minimal quantities of allergen and serum [2]. However, to achieve an accurate diagnostic assessment, it is still important to apply an adequate panel of allergens [3].

The ImmunoCAP ISAC 112 microarray (Thermo Fisher Scientific) is the only commercially available allergenic protein microarray, but its current panel of allergens does not seem to have the best accuracy when it comes to diagnosing food or pollen allergies in certain regions [3]. Indeed, some authors have even suggested including other allergens [3,4]. As part of the Spanish National Research Network of adverse reactions to allergens and drugs (RIRAAF), our team recently developed a new allergenic protein microarray model.

The aim of this study was to compare the diagnostic performance of the commercial ISAC 112 microarray and the RIRAAF microarray for the study of allergies to certain fruit (peach, apple, kiwifruit), olive pollens, and nuts in a Mediterranean area.

We prospectively enrolled 101 patients with a consistent history of an IgE-dependent reaction to peach (n=35), apple (n=16), kiwi (n=7), peanut (n=18), hazelnut (n=15), and/or walnut (n=19), a positive skin prick test (ALK-Abelló, Madrid, Spain), and sIgE (ImmunoCAP) to the relevant allergen sources. We also enrolled 53 patients with olive pollen allergy (rhinoconjunctivitis and/or asthma during the olive pollen season) and 28 controls. All participants were selected from the 14 participating Spanish hospitals. The research ethics committees of the participating hospitals approved the study.

The determination of sIgE to 112 natural (n) or recombinant (r) allergens was performed using ImmunoCAP ISAC 112 in all individuals following the manufacturer's recommendations; sIgE was considered to be positive when the ISU value was ≥0.3.

The RIRAAF microarray was applied by printing and duplicating the purified allergenic proteins (nPru p 2.2, nAct d 1, nAct d 2 [5], rPru p 3, rMal d 3, nJug r 3, nCor a 8 [6], nAra h 1, nAra h 2, nAra h 9 [7], nOle e 1, Ole e 7, and Ole e 9 [8]), which were then fixed on glass slides (concentration, 0.25 µg/µL) together with different concentrations of human IgE used to build a control curve. Sera pertaining to both study and control individuals were hybridized after overnight incubation at 4ºC. A murine anti-IgE antibody marked with Alexa-456 was used as a secondary antibody. The slides were scanned by ScanArray Express (PerkinElmer). The study results were expressed as a signal noise ratio (SNR) fluorescence intensity for each allergen. The SNR was considered to be positive when the value was 3 or greater (mean+2SD of controls).

Sensitivity, specificity, positive and negative predictive values, and correct classification of each patient's parameters were determined for both the ISAC and RIRAAF microarrays in order to evaluate their ability to discriminate between

Table. Diagnostic Capacity of Microarray Platforms ISAC 112 and RIRAAF Showing Results for Individual Allergens and Allergens From Same Source

Allergen	Platform	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Cor Class	AUC	P Value[a]
Act d 1	ISAC	57.1	96.4	80.0	90.0	88.6	0.768	.028[b]
	RIRAAF	14.3	92.8	17.7	68.3	77.1	0.535	
Act d 2	ISAC	14.3	100.0	100.0	82.5	82.8	0.571	.999
	RIRAAF	28.6	85.7	33.3	82.7	74.2	0.571	
Act d 5	ISAC	14.3	100.0	100.0	82.4	82.3	0.508	
Act d 8	ISAC	0.0	100.0		80.0	80.0	0.500	
Kiwi allergens	ISAC	71.4	96.4	83.3	93.1	91.4	0.839	.006[b]
	RIRAAF	28.6	78.6	25.0	81.5	68.6	0.536	
Ara h 1	ISAC	0.0	100.0		60.8	60.8	0.520	.613
	RIRAAF	16.6	82.1	37.5	60.5	56.5	0.494	
Ara h 2	ISAC	0.0	100.0		60.8	60.8	0.520	.167
	RIRAAF	0.0	96.4	0.0	60.0	58.7	0.482	
Ara h 3	ISAC	0.0	100.0		60.9	60.9	0.500	
Ara h 6	ISAC	11.1	100.0	100.0	63.6	63.8	0.500	
Ara h8	ISAC	0.0	100.0		60.9	60.9	0.500	
Ara h 9	ISAC	61.1	100.0	100.0	80.0	84.8	0.805	.630
	RIRAAF	61.1	92.8	84.6	78.8	80.4	0.770	
Peanut allergens	ISAC	61.1	100.0	100.0	80.0	84.8	0.805	.259
	RIRAAF	66.6	75.0	63.1	77.7	71.7	0.708	
Cor a 1	ISAC	0.0	100.0		65.1	65.1	0.500	
Cor a 8	ISAC	66.6	96.4	90.9	84.4	86.0	0.815	.046[b]
	RIRAAF	33.3	96.4	83.3	73.0	74.4	0.649	
Cor a 9	ISAC	6.7	100.0	100.0	66.7	67.4	0.500	
Hazelnut allergens	ISAC	73.3	96.4	91.7	87.1	88.4	0.849	.004[b]
	RIRAAF	33.3	96.4	83.3	73.0	74.4	0.649	
Jug r 1	ISAC	5.3	100.0	100.0	60.9	61.7	0.500	
Jug r 2	ISAC	5.3	96.4	50.0	60.0	59.6	0.508	
Jug r 3	ISAC	73.7	92.8	87.5	83.9	85.1	0.833	.007[b]
	RIRAAF	26.3	100.0	100.0	66.7	70.2	0.631	
Walnut allergens	ISAC	84.2	89.3	84.2	89.3	87.2	0.867	<.001[b]
	RIRAAF	26.3	100.0	100.0	66.7	70.2	0.631	
Pru p 1	ISAC	8.6	100.0	100.0	46.7	49.2	0.500	
Pru p 2	RIRAAF	5.7	92.9	50.0	44.1	44.4	0.507	
Pru p 3	ISAC	85.1	96.4	96.7	84.4	90.5	0.911	<.001[b]
	RIRAAF	28.6	96.4	90.9	51.9	58.7	0.625	
Peach allergens	ISAC	88.6	96.4	96.8	87.1	92.0	0.925	<.001[b]
	RIRAAF	31.4	89.3	78.6	51.0	57.1	0.603	
Mal d 1	ISAC	18.8	100.0	100.0	68.3	70.4	0.594	
Mal d 3	RIRAAF	37.5	92.8	75.0	72.2	72.7	0.652	
Apple allergens	ISAC	18.8	100.0	100.0	68.3	70.4	0.594	.497
	RIRAAF	37.5	92.8	75.0	72.2	72.7	0.652	
Ole e 1	ISAC	81.1	82.1	89.6	62.7	81.5	0.816	.067
	RIRAAF	64.1	78.6	85.0	53.7	69.1	0.714	
Ole e 7	ISAC	15.1	100.0	100.0	38.3	44.4	0.575	.010[b]
	RIRAAF	0.0	100.0		34.6	34.6	0.509	
Ole e 9	ISAC	7.5	100.0	100.0	36.3	39.5	0.538	.665
	RIRAAF	11.3	92.8	75.0	35.6	39.5	0.521	
Olive allergens	ISAC	83.0	82.1	89.8	71.9	82.7	0.826	.070
	RIRAAF	67.9	75.0	83.7	55.2	70.4	0.715	

Abbreviations: AUC, area under receiver operating characteristic curve; Corr class, correctly classified patients; NPV, negative predictive values; PPV, positive predictive values; Sens, sensitivity; Spec, specificity.
[a]Comparative significance between AUC values for ISAC and RIRAAF microarrays.
[b]Significant values (P<.05).

symptomatic patients and controls. The resulting areas under the receiver operating characteristic curve (AUC) for the allergens studied were assessed both individually and globally for the same allergenic source, and AUC values were compared between platforms (Table).

Compared with the RIRAAF microarray, the ISAC platform showed a greater ability to detect sIgE to peach, kiwifruit, hazelnut, and walnut. In fact, better sensitivity values were observed for the allergens Act d 1, Cor a 8, Jug r 3, and Pru p 3 with the ISAC microarray.

The ISAC microarray also performed better at detecting sensitization to olive pollen, probably in relation to the higher sensitivity observed for Ole e 1 in this platform, although the differences with the RIRAAF microarray were not statistically significant.

Both microarrays showed similar diagnostic ability for the detection of apple allergy. However, the RIRAAF microarray identified a greater number of cases due to the presence of Mal d 3, a lipid transfer protein (LTP) and the major apple allergen in our region. Mal d 1 is the only apple component in ISAC and is a minor allergen in our country [9].

Finally, peanut allergy was diagnosed similarly by both platforms, although the ISAC microarray detected sIgE to 3 more allergens than the RIRAAF microarray (Ara h 3, Ara h 6, and Ara h 8), suggesting their low relevance in our population.

We have described a new diagnostic tool that includes the major allergens of the studied foods [10] and of olive pollen in the Mediterranean basin. Although the RIRAAF microarray showed a greater ability to diagnose apple allergy, its sensitivity for the rest of the allergies studied was lower than that of ISAC. Despite the application of this LTP-rich panel, which may facilitate a better approach to patients in our region, the sensitivity of the RIRAAF microarray was lower than that of ISAC for most allergens. A similar sensitivity was found only for Ara h 9.

Different assays in previous studies by our team have shown good accuracy for most of the allergens on the RIRAAF platform [5-8]. However, its sensitivity might have been affected by suboptimal adherence of the allergens to the platform, possibly due to the formation of allergen-buffer complexes or to the lack of an individualized concentration for each allergen.

Despite the application of a well-chosen panel of allergens that allows for a better assessment of molecular sensitization according to the geographical origin of patients, we consider that multiplex platforms should be technically optimized in order to ensure better diagnostic performance. Moreover, further studies are needed to evaluate the usefulness of the commercial ISAC microarray for the diagnosis of other allergies.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Does the Profile of Sensitization to Grass Pollen Allergens Have Clinical Relevance?

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Key words: Recombinant allergens. Molecular diagnosis. Grass pollen allergy. Allergic rhinoconjunctivitis and asthma.

Palabras clave: Alérgenos recombinantes. Diagnóstico molecular. Alergia a polen de gramíneas. Rinoconjuntivitis y asma alérgicas.

Grass pollen is the most common cause of seasonal respiratory allergy worldwide, and affects 8% to 25% of the general population [1-2]. In recent years, component-resolved diagnosis (CRD) using measurements of specific IgE to individual allergens (either natural or recombinant) is being increasingly used. CRD has improved the diagnostic work-up of allergy to pollen, allowing more accurate evaluation of sensitization profiles and differentiation between true cosensitization and cross-reactivity to pollen allergens [3]. Several allergenic components are available for CRD of grass pollen allergy (*Phleum pratense*). The most widely used components are rPhl p 1 and rPhl p 5, as markers of genuine sensitization, and rPhl p 12 (profilin) and rPhl p 7 (polcalcin), as panallergens considered responsible for cross-reactivity with other pollens [4-5]. However, the clinical implications of sensitization patterns to different pollen allergens in sensitized patients are unknown.

In the present study we evaluated the profile of sensitization to recombinant grass pollen allergens and explored its potential association with different clinical features among patients allergic to grass pollen living in the northern area of Madrid, Spain. The study was approved by the local ethics committee (HULP PI-1682).

In this retrospective study, we included 248 patients diagnosed with grass pollen allergy in the previous year; they had a positive skin prick test to mixed grass pollen extract (ALK-Abelló, Madrid, Spain) and positive specific IgE measurement (>0.35 kU/L) to at least 1 of the following recombinant allergens: rPhl p 1, rPhl p 5, rPhl 7, and rPhl p 12 (InmunoCAP, Thermo Fisher Scientific). The patients (132 men) ranged in age from 3 to 68 years old (mean age, 21.3) and 85.9% were white (Hispanic, 10.1%).

A family history of atopy was found in 46.4% of patients. Rhinitis was the most frequent disorder (97.6%) and was commonly associated with conjunctivitis (96%). Most patients (84.7%) had persistent rhinitis, and 186 (75%) had asthma, which was persistent in 79% of cases and controlled in 64.5%. Demographic data are summarized in the Table. The mean duration of rhinitis and asthma was 5.83 and 5.81 years, respectively. Median forced expiratory volume in the first second (% predicted) in the pollen season was 100% (range, 57%-144%), and median total serum IgE was 281 kU/L (range, 27-1865 kU/L). Of the 248 patients studied, 244 (98%) were sensitized to rPhl p 1 (median, 26.1 kU/L; range, 0.39-101 kU/L), 141 (56.8%) to rPhl p 5 (median, 16.5 kU/L; range, 0.38-101 kU/L), 35 (14.1%) to rPhl p 12 (median, 7.36; range, 0.36-69 kU/L), and 11 (4.4%) to rPhl p 7 (median, 4.73; range, 0.51-100 kU/L).

Ninety-three percent of the study population were sensitized to pollens other than grasses (average of 3 pollen sources) and 53.3% were sensitized to animal dander (37.8%, dog; 15.5%, cat; 7.7%, horse; and 1.6%, hamster). Sensitization to house dust mites and molds was found in 26.2% and 17.7% of patients, respectively.

No association was found between different sensitization patterns to grass pollen allergens and clinical features of asthma or rhinitis (severity, control, duration, etc.). The only significant association observed was between the progression of rhinitis to asthma and longer duration of rhinitis (*P*=.012). A numerical trend approaching statistical significance was observed between being sensitized to rPhl p 1 and the presence of asthma (*P*=.054). A significant positive correlation was observed between age and duration of rhinitis/asthma (Pearson correlation coefficients of 0.561 and 0.568, respectively), and a negative relationship was observed between sensitization to rPhl p 1 and duration of both disorders (-1.118 and -1.181 respectively). Surprisingly, no association was found between severity of rhinitis and asthma, although the development of asthma was associated with a longer duration of rhinitis. Moreover, there was little difference between the duration of both diseases, possibly in relation to the characteristics of the study population (all referred to a tertiary hospital).

Between 50% and 80% of patients referred to an allergist in Spain are polysensitized [6]. Identification of the relevant allergen can be difficult in patients sensitized to various pollens in areas with overlapping pollen seasons. In one Spanish study, of 99.4% of patients allergic to grass pollen who were polysensitized to unrelated pollens according to CRD with rPhl p 1, rPhl p 5, rPhl p 7, and rPhl p 12, only 36% were considered to be truly polysensitized after allergenic cross-reactivity had been ruled out [7]. In our study, considering that sensitization to profilin (rPhl p 12) was present in 14.1% of patients and sensitization to polcalcin (rPhl p 7) in 4.4%, CRD might be helpful for prescribing immunotherapy in these patients[8], but, overall, it alone cannot justify the high rate of polysensitized patients detected. It is noteworthy that 86.8% of patients had persistent rhinitis, which could be explained by the high frequency of polysensitization in this population sample. It is also worth remarking that in children, the prevalence of sensitization to rPhl p 5 was lower than in adults, as previously described by Scaparrotta et al [9] in a study of 207 children under 10 years of age.

Savi et al [10] found a significant association between severe persistent rhinitis and the presence of asthma and, in keeping with our results, no correlation was observed between

severity of rhinitis and levels of specific IgE to rPhl p 1, rPhl p 5, rPhl p 7, or rPhl p 12. Only low levels of specific IgE to rPhl p 5 were associated with the absence of asthma in patients allergic to grass pollen. By contrast, in our study we found no evidence to suggest that asthma is associated with a particular sensitization profile. Furthermore, although a numerical trend showed that being sensitized to rPhl p 1 may be associated with the development of asthma, this observation could also be explained by the fact that rPhl p 1 IgE levels are also significantly associated with duration of allergic respiratory disease and, therefore, with longer duration of exposure to grass pollen.

In conclusion, we did not identify any relationship between the molecular sensitization profile and clinical features of respiratory allergy in this population. Only higher IgE levels to rPhl p 1 seem to be associated with longer disease duration.

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Conflicts of Interest

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Non-asthmatic Eosinophilic Bronchitis and Idiopathic Eosinophilic Esophagitis

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Non-asthmatic eosinophilic bronchitis (NAEB), which was first described by Gibson et al [1] in 1989, is now considered a relatively common cause of chronic cough. It is characterized by persistent dry cough, with little or abundant sputum, and bronchial eosinophilic inflammation (similar to that seen in asthma) with sputum eosinophilia equal to or greater than 3%. Unlike asthma, bronchial hyperresponsiveness is not observed in pulmonary function tests [1,2].

Eosinophilic esophagitis (EoE) in adults was described as a separate clinicopathological entity by Attwood et al [3] in 1993. It has been defined as an antigen-mediated chronic esophageal disease characterized by symptoms of esophageal dysfunction and predominant eosinophilic inflammation, with at least 15 eosinophils per high-power field (eos/hpf) [4].

We report an unusual case of NAEB and EoE coexisting in the same patient characterized by eosinophilic inflammation and involvement of 2 organs (bronchi and esophagus). A 47-year-old man working as a clerk in an optician´s where glasses were sold but not repaired was referred to our allergy department for consultation. He had a history of factitious urticaria and good response to oral antihistamines and reported gastrointestinal symptoms of 2 years' duration, consisting of dyspepsia and dysphagia for solid foods, without clear signs of choking, and chest pain unrelated to food intake. He also had respiratory symptoms, including sneezing, nasal congestion, and itchy eyes, nose, and throat, accompanied by dry cough and slight dyspnea without audible wheezing. The cardiopulmonary and abdominal examination was normal. A routine analytical work-up detected blood eosinophilia of 1560 eos/mcL, which 6 months later decreased to 492 eos/mcL. Serology for hepatitis B and C virus, human immunodeficiency virus, and fecal parasites were within normal ranges. The electrocardiogram showed a sinus rhythm of 65 bpm, and the chest x-ray showed no significant alterations.

Upper endoscopy showed over 50 eos/hpf in the proximal and distal esophageal segment and 10 eos/hpf in the middle segment; no eosinophils were detected in the stomach or duodenum. Treatment with omeprazole 80 mg/d was prescribed for 2 months, after which a new esophagoscopy showed over 50 eos/hpf in the 3 esophageal sections.

Skin prick tests were performed with common aeroallergens consisting of pollens (grass, olive, Cupressaceae, *Platanus acerifolia*, Chenopodiaceae), mites, molds, and cat and dog dander. They were positive for grass (3x3 mm), olive (4x4 mm), *Dermatophagoides pteronyssinus* (5x3 mm), and *Dermatophagoides farinae* (4x3 mm). Skin prick tests with food—wheat, lentils, peanuts, eggs, milk, hake, shrimp, lipid transfer protein, and profilin—were negative.

Total IgE was 214 kU/L and specific IgE (sIgE) values, measured by ImmunoCAP, were 3.01 kU/L for Ole e 1, 3.32 kU/L for *D pteronyssinus*, 2.04 kU/L for *D farinae*, 1.48 kU/L for milk, 1.16 kU/L for wheat, 0.95 kU/L for peanut, and 0.62 kU/L for lentil. sIgE for shrimp, hake, and egg were all under 0.35 kU/L. Baseline forced spirometry and a post-bronchodilator test were normal. A methacholine challenge using the semiabbreviated Chai method [5] was negative up to 400 IU. We did not perform a bronchial hyperreactivity test with adenosine because its use is not allowed in humans. Spontaneous sputum cytology showed 80% eosinophils, 17% epithelial cells, 1% erythrocytes, and 2% neutrophils.

The patient was diagnosed with EoE and prescribed an elimination diet of grains, legumes, nuts, and milk, based on the allergy test results. After 6 weeks, the esophagoscopy was repeated and over 30 eos/hpf persisted in the 3 esophageal segments. An empirical elimination diet with 6 food groups was extended for an additional 6 weeks, after which a new esophagoscopy detected over 50 eos/hpf in the lower section and 6 eos/hpf in the upper section.

We established a diagnosis of mild allergic rhinoconjunctivitis due to mites and pollens, eosinophilic bronchitis, and idiopathic eosinophilic esophagitis. The patient's rhinoconjunctivitis did not require treatment with antihistamines, and his cough subsided after 2 months of treatment with budesonide 400 mcg/12 h, with no recurrence in subsequent months. The patient reported only intermittent retrosternal chest pain.

We have described the presence of 2 rare clinical entities in the same patient: EoE and NAEB. The relatively recent description of both diseases [1,3] might explain why underdiagnosis is still common. Both conditions affect middle-aged individuals [2,6], but EoE is more common in atopic men [2,4,6].

Despite our exhaustive studies, we were unable to detect the cause of either disease. A chronic cough of 2 years' duration requires ruling out the involvement of house dust mites. This condition, however, is unlikely because our patient lives in a central part of Spain with a dry, extreme climate where patients sensitized to mites usually only experience mild symptoms in spring and autumn. If mites were the causative agent, we would expect to see improvement in cough and dysphagia symptoms in summer and winter. We ruled out the involvement of grass

and olive pollens because these allergens are present only in spring. We also considered the possibility of occupational exposure [7-9] for both NAEB and EoE, but after a thorough medical history, we found no relationship between symptoms of either disease with the patient's work or, indeed, hobbies. We were unable to determine whether the EoE in our patient was caused by food allergens or inhaled allergens, although the former route is more common [7,10].

NAEB improved clinically with inhaled topical corticosteroids [2], which not only led to a very significant reduction in sputum eosinophils but also decreased the intensity and sensitivity of the cough reflex. We also observed a reduction in bronchial hyperreactivity, although this was always within the normal range [2]. EoE did not remit after an elimination diet based on the allergy test results or after a subsequent 6-food elimination diet [10].

We think that the persistent and intermittent retrosternal chest pain in our patient may be secondary to his esophageal dysfunction, since the EoE did not go into remission [6].

Our patient had significant peripheral eosinophilia (1560 eos/mcL) alternating with mild eosinophilia (492 eos/mcL) before treatment with inhaled corticosteroids and elimination diets, probably in relation to his atopic condition.

We have presented the first report of a patient with mild atopic peripheral eosinophilia who was simultaneously diagnosed with idiopathic NAEB and idiopathic EoE.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Pollen Counts Influence Web Searches for Asthma and Rhinitis

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Asthma and allergic rhinitis (AR) represent a major health problem, as both diseases are relatively common and cause significant symptoms that interfere with the lives of those affected [1,2]. In Portugal, asthma affects approximately 7% of the population [1], while AR affects up to 26% [2]. Aeroallergens are common asthma and AR triggers [3] and are usually classified as indoor, outdoor (pollens and molds), or occupational [4]. Previous studies have confirmed the association between pollen levels and asthma-related emergency department visits [5], but no data are available on other resources used by patients. Google Trends (GT) is a web-based search tool that indicates trends related to specific Google queries over a defined period of time [6]. Its utility in allergic disease monitoring has been evaluated only in terms of the relationship between total pollen counts and rhinitis and only in relation to searches in English and German [7,8]. No studies to our knowledge have analyzed GT search trends for asthma, other languages, or individual pollens. The aim of this study was to explore the correlation between pollen counts and GT searches for asthma, rhinitis, and the main pollens associated with these diseases.

We conducted an ecological study using web and pollen count data available for Lisbon (Portugal) from 2007 to 2012 (6 years). Pollen count data were collected from Lisbon´s monitoring station (Mediterranean climate; Csa Köppen-Geiger Climate Classification). Counts and concentrations were analyzed using the Hirst volumetric method, following a standardized protocol from the International Association of Aerobiology. The following pollens were analyzed: *Betulaceae, Castanea, Chenopodiaceae, Compositae, Cupressaceae, Myrtaceae, Olea, Palmae, Parietaria, Pinaceae, Plantago,*

Platanus, Poaceae, Quercus suber, Quercus, Rumex, Salix, Umbelliferae, and *Urtica*. GT works by analyzing how many Google searches are done for the terms entered relative to the total number of searches in the same time period and region. GT results were extracted for rhinitis and asthma search terms in the Lisbon region from 2007 to 2012. As the GT search index was only available for monthly periods, we calculated average monthly pollen counts based on the daily data available. Total pollen count trends were transformed using a similar methodology to that of GT to allow comparisons with GT indices and to present the results graphically using a scale of 0 (minimum during study period) to 1 (maximum) [6]. The pollen count index at a specific time point corresponds to the ratio between pollen counts at that point and maximum pollen counts during the study period. Subsequently, GT results for rhinitis and asthma were correlated with total pollen counts using Spearman's rank-order correlation, after confirming a monotonic relationship. Pollens with peak levels lower than 30 grains/m^3—the clinically relevant cutoff—were excluded. Spearman's rank-order correlation coefficients were categorized as follows: 1-0.75, strong correlation; 0.75-0.25, moderate correlation; and 0.1-0.25, weak correlation. A significance level of α=0.05 was used although P values of over .05 and under .10 were also considered.

From 2007 to 2012, the median total pollen count was 43.8 grains/m^3/mo (interquartile range, 19.8-200.3 grains/m^3/mo). The main pollens identified in the study period, expressed as a percentage of total pollens, were *Urtica* (18.3%), *Cupressaceae* (15.1%), *Olea* (12.9%), *Parietaria* (10.9%), and *Quercus* (10.2%). Total pollen counts and search trends for rhinitis showed a cyclical seasonal pattern, with peaks in spring months (March-June). Asthma search trends showed a similar, though less pronounced, pattern. Total pollen counts and search trends for asthma and rhinitis during the study period are presented in the Figure. Total pollen count had a statistically significant positive correlation with the GT search index for rhinitis (r=0.366; P=.002; moderate) and asthma (r=0.305; P=.009; moderate). The following pollens, based on the cutoff of over 30 grains/m^3, were analyzed in GT: *Cupressacea, Olea, Parietaria, Platanus, Poaceae, Quercus suber, Quercus*, and *Urtica*. Individual pollen counts with a statistically significant correlation with the GT search index for asthma were *Cupressaceae* (r=0.402; P<.001; moderate), *Platanus* (r=0.255; P=.031; moderate), *Quercus* (r=0.337; P=.004; moderate), and *Urtica* (r=0.432; P<.001; moderate). The same individual pollens were identified for rhinitis: *Cupressaceae* (r=0.461, P<.001, moderate), *Platanus* (r=0.285, P=.015, moderate); *Quercus* (r=0.231, P=.051, weak); and *Urtica* (r=0.431, P<.001, moderate).

The pollen levels and main pollen species identified in this study are comparable to findings previously reported for Lisbon and Mediterranean areas of Europe [9]. Associations between total pollen counts and web searches for rhinitis have been previously reported [7,8], although this is the first study to compare searches in a language other than English or German and in an area with a Mediterranean climate. Moreover, to the best of our knowledge, our study is the first to analyze the correlation between specific pollens and web searches for asthma and rhinitis. A weaker though still significant
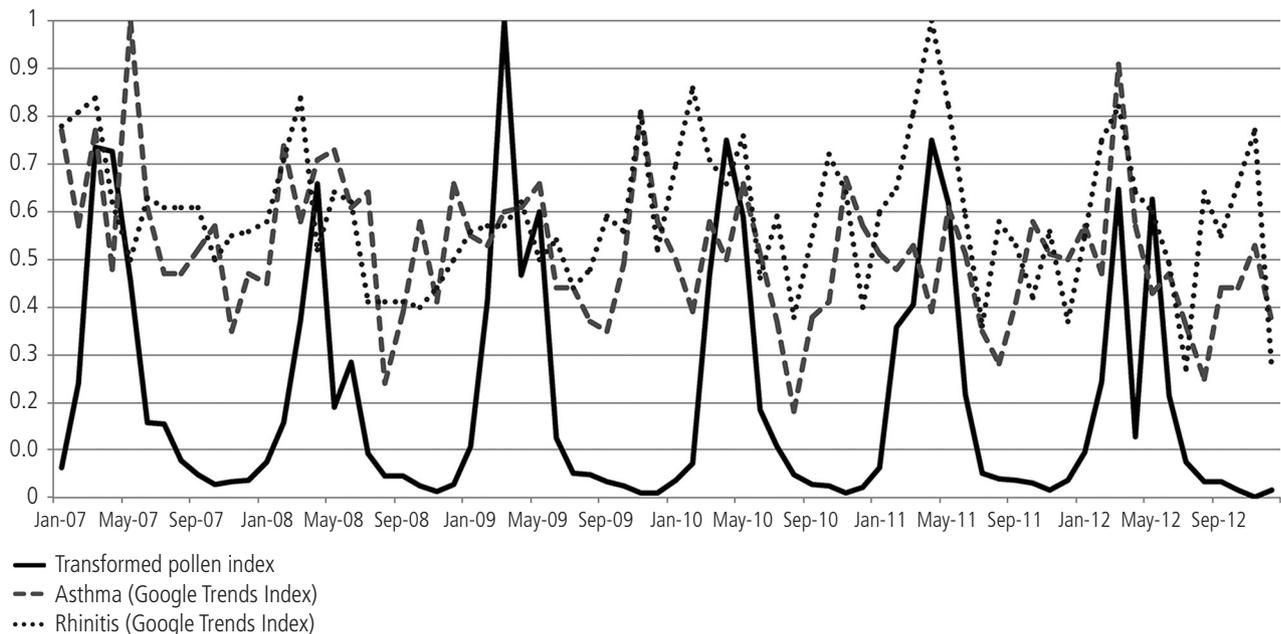
Figure. Total pollen counts and Google Trends search indices for asthma and rhinitis during study period (2007-2012).

correlation was found between total pollen counts and the GT search index for asthma. One possible explanation for this weaker correlation is that the second peak period detected in winter months was probably associated with respiratory infections, an important asthma trigger [3]. The specific pollens that were significantly and positively correlated with web searches for rhinitis and asthma (*Cupressaceae, Platanus, Quercus,* and *Urtica*) are not a common cause of respiratory allergic disease in Portugal. Several explanations for this discrepancy are possible, including the fact that pollens contain different components that can stimulate an innate immune response [10] and that these pollens are more "visible", perhaps bringing patients to believe that they are responsible for their symptoms.

Our results indicate that patients with AR and asthma seek information about their diseases on the Internet, especially in pollen seasons. Little, however, is known about which online sources patients use for this purpose. As the preferential, or top-ranking, websites identified by search engine algorithms could be erroneous, special attention should be paid to the reliability and quality of websites providing medical information.

In conclusion, total pollen counts are significantly correlated with web searches for information on rhinitis and asthma, independently of the search language or climate area. Website monitoring is important for patients and the medical community and GT may constitute an essential tool for predicting asthma and AR outbreaks.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Electroconvulsive Therapy in Patients with C1 Inhibitor Deficiency: A Major or Minor Procedure?

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Electroconvulsive therapy (ECT) has been used for the treatment of psychiatric conditions since the 1940s. Although considered controversial in the past, ECT has proven acceptable for specific conditions [1]. Nowadays, it is indicated for severe depression, schizophrenia, bipolar disorder, and schizoaffective disorder. The procedure involves application of a small electric current to produce a generalized cerebral seizure under general anesthesia and is repeated at least 6 to 8 times before evaluating the clinical response [2].

Hereditary angioedema (HAE) is a genetic defect caused by a lack of the protein C1 esterase inhibitor (C1-INH). Consequently, the body does not produce sufficient quantities of the protein (type 1 HAE) or the protein generated does not function (type 2 HAE) [3]. The disease progresses with episodes of angioedema that affect the respiratory system and may be life-threatening. Angioedema attacks can be induced by physical trauma, including invasive medical or surgical procedures [4]. Clinical guidelines for management of HAE recommend short-term prophylaxis before performing these procedures. The type of prophylaxis depends on the procedure (major or minor) and the patient [5,6]. There is no previous published experience of management of HAE C1-INH in patients who require ECT. Therefore, the technique has not been classified as a minor or a major procedure.

We present our experience in the management of a 57-year-old woman with HAE who was prescribed ECT for major depression. The patient was referred to the Allergy Department of Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain in 2004 because of monthly episodes of swelling in her feet and hands since she was 16. In addition, she had experienced repeated episodes of abdominal pain, and laparotomy revealed no significant findings.

C1-INH levels and activity were below normal values in at least 2 determinations, and a diagnosis of HAE was established. Treatment with stanozolol 2 mg daily was initiated, and the patient's condition gradually improved. The frequency and severity of the attacks decreased considerably to ≤1 mild episode per year, with no need to visit the emergency department or receive purified C1-INH.

In 2008, the patient was diagnosed with depression in the psychiatry department. She received several drugs, but her status worsened and progressed to treatment-refractory major depression. ECT was recommended.

ECT procedures were performed under the constant supervision of a psychiatrist, anesthesiologist, and allergist. After ECT, the patient was admitted to the postanesthesiology area for a 10-hour observation period. Purified C1-INH was always on hand.

ECT was initially considered a major procedure because of our lack of experience and the absence of previous medical reports in a Medline search. The dose of stanozolol was increased to 2 mg tid for 5 days before the procedure. The patient continued with this dose while she was receiving ECT. For the first procedure, she was admitted to hospital and received 2 doses (1000 IU and 500 IU) of purified C1-INH (Berinert, CLS Behring) 6 hours and 30 minutes before ECT. Additional doses of C1-INH were always available in the operating room and in the recovery area. After ECT, the patient was admitted to the postanesthesiology area. She was discharged home after an observation period of 10 hours. There were no incidents during the procedure or at home. Therefore, we decided that the procedure could be considered low-risk. The dose of purified C1-INH was reduced. For the second procedure, she received only 1 dose of C1-INH (500 mg) 30 minutes before the ECT. There were no incidents.

The third procedure was carried out without purified C1. No incidents were reported. The following procedures were also carried out with a single 500-mg dose of C1-INH 30 minutes before the ECT. Again, no incidents were reported. The patient received 1 session each week for a total of 8 sessions.

Once the patient's psychiatrist decided to finish ECT, we decreased the dose of stanozolol again to 2 mg. No subsequent incidents were reported.

ECT is considered a risky procedure. It is performed under general anesthesia owing to the possibility of trauma during surgery. The most common complications are cardiovascular respiratory events, trauma, agitation, confusion, headache, nausea, and vomiting [7]. We were unable to find previous reports of patients diagnosed with HAE who have received ECT. ECT can trigger angioedema attacks. Initially, we considered the procedure to be high-risk, similar to major surgery [4]. However, given the absence of complications during the initial sessions, we considered ECT a minor procedure and did not administer purified C1-INH. The result was satisfactory in terms of control of symptoms and prevention of angioedema attacks.

In conclusion, ECT can be considered a low-risk procedure in patients with optimal disease control. It is useful to increase the doses of the patient's usual treatment, as in a minor procedure. C1-INH should be available in the room where the procedure is performed. Given the lack of experience with this type of patient, the use of C1-INH should be individualized to prevent angioedema attacks.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Nonoccupational Airborne-Induced Anaphylaxis Caused by *Anisakis simplex*

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Anisakis simplex, a parasitic nematode found in fish and cephalopods, causes a wide spectrum of clinical conditions, including occupational respiratory diseases, contact dermatitis, and anaphylaxis [1-4]. Anaphylaxis due to airborne exposure is relatively uncommon and only a few etiological agents have been described so far. These include worms, latex, o-(benzotriazol-1-yl)-N,N,N9,N9-tetramethyluronium hexafluorophosphate (HBTU), peanuts, cow's milk, fish, and common fig [5-9]. *Anisakis* has been described as an occupational cause of airborne anaphylaxis [10], but no cases of non-occupational anaphylaxis triggered by airborne exposure to this allergen have yet been described.

We report the case of a 36-year-old nonatopic woman, working as a cleaner, who had experienced urticaria and angioedema after eating fresh anchovy for several years. She had also had 1 episode of contact urticaria after touching fresh mussel shells. In 2009, she developed rhinoconjunctivitis followed by generalized pruritus, tongue edema, cough, dyspnea, and dizziness while standing on the street, just in front of a fish store. The episode resolved spontaneously in about 60 minutes. This systemic reaction has reoccurred on many occasions following different airborne exposures, such as standing in front of a fish store, handling fish, and/or inhaling vapors during the cooking of fish. She reported that she had never experienced any reactions on eating frozen, fresh, or cooked fish or shellfish. She had, however, avoided eating all seafood since she had experienced her last systemic reaction. She worked as a cleaner in public buildings and to her knowledge had never come in contact with fish or fish vapors potentially infested with *Anisakis* while working. A specific allergological work-up was performed.

Skin prick tests (SPTs) were performed with a standard series of aeroallergens (house dust mites, fungal spores, grass, weed and tree pollens, cat, and dog dander), food allergens (*Anisakis*, milk, egg, cereals, fruits, nuts, vegetables, legumes, and lipid transfer protein), and latex (ALK-Abelló, Madrid, Spain). The positive and negative controls used were histamine (10 mg/mL) and phenolated glycerol saline, respectively. A reaction with a hive diameter greater than 3 mm compared with the negative control was considered positive [3]. The SPTs were positive only to *Anisakis*. The rest of the anaphylaxis protocol was negative, including stool tests for parasites and hydatidosis serology. Considering the contact urticaria the patient had experienced after touching fresh mussel shells, we also performed a series of tests to rule out allergies other than *Anisakis*. These included SPTs and prick to prick tests with different fish and shellfish (hake, sole, cod, sardine, anchovy, salmon, tuna, squid, shrimp, clam, mussel, and oyster). The results were negative in all cases. Serum specific IgE (sIgE) against fish, crustaceans, molluscs (including mussel), and latex were less than $0.10 \, kU_A/L$ (negative, $<0.35 \, kU_A/L$) (ImmunoCAP, Thermo Fisher Scientific). However, sIgE against clam was positive ($5.97 \, kU_A/L$), with a total IgE of 7490 IU/mL (normal, <100 IU/mL); *Anisakis* sIgE was over $100 \, kU_A/L$ (Table). sIgE levels to tropomyosins (Pen a 1, Der p 10) and parvalbumins (Gad c 1, Cyp c 1) were $0.01 \, kU_A/L$. To investigate possible cross-reactivity between *Anisakis* and *Ascaris* and the high total serum IgE detected, we performed serum sIgE determination against *Ascaris*, which was negative ($<0.10 \, kU_A/L$). Serum baseline tryptase levels were 5.7 and 6.1 µg/L (normal, <11.4 µg/L). Oral food challenges with hake, sole, tuna, squid, shrimp, mussel, and clam under anti-*Anisakis* conditions (frozen at -20º C for at least 48 hours) were well tolerated. We therefore ruled out fish and shellfish allergy.

The positive SPT to *Anisakis* and the repeatedly positive sIgE against *Anisakis* over 4 years confirmed sensitization to this nematode (Table). Nevertheless, allergy to *Anisakis* is overdiagnosed, and to further assess a direct link between exposure to *Anisakis* and the patient's symptoms, we performed a specific inhalation challenge (SIC). We placed the patient in a 70-m^3 room where a volunteer manipulated trays containing different fresh fish species, resembling a real situation in a fish store. Two additional volunteers (1 atopic and 1 nonatopic) served as controls; they were placed next to the patient, and all 3 were at a distance of 2 meters from the volunteer handler. Informed consent was obtained from all 4 people prior to the SIC. After 5 minutes of exposure, our patient developed intense sneezing, rhinorrhea, conjunctivitis, and a pruritic micropapular erythema on her face. Intramuscular 6-methyl-prednisolone and dexchlorpheniramine were administered immediately, and the symptoms disappeared completely in 30 minutes. Neither of the control volunteers showed symptoms. The only occupational case of *Anisakis*-induced anaphylaxis described so far was established without an SIC [10]. The patient was a woman working in a frozen-fish factory who developed symptoms after handling fish and inhaling fish cooking vapors. These symptoms disappeared immediately on removing the source of occupational exposure. The episode of contact urticaria experienced by our patient after touching fresh mussel shells was attributed to direct contamination by *Anisakis*-infested fish that could have come into contact with these shells in the fish store. Finally, eosinophil values were not associated with IgE levels against *Anisakis* (Table). If the patient had had a concomitant parasitic infection, these values should have been altered.

The recurrence rate of anaphylaxis is 2 to 3 times lower in the case of anaphylaxis without an associated atopic disease (*Anisakis* and drugs) than in anaphylaxis with such a disease (food, latex, and exercise) [4]. This is because the former is

Table. Chronological Data Showing Serum Total IgE, Specific IgE against *Anisakis*, and Peripheral Blood Eosinophil Levels (% and cells/mm^3)

Date of Blood Test	Serum Total IgE (IU/mL)	Serum Specific IgE Against Anisakis (kU$_A$/L)	Peripheral Blood Eosinophils (%)	Peripheral Blood Eosinophils (cells/mm^3)
30 December 2009	7490	>100	9.2	690
9 April 2010	2850	>100	6.4	550
9 November 2010	715	99.7	4.1	390
24 June 2011	530	55.7	7.7	600
21 February 2013	346	47.6	5.7	510
4 April 2013	238	25.7	6.0	530
25 June 2013	291	20.2	7.9	620
4 July 2013	353	19.0	5.6	500
24 September 2013	302	21.4	5.3	470
4 December 2013	290	18.0	7.3	580
20 June 2014	229	12.5	6.7	600
6 February 2015	240	10.7	4.4	490

easier to avoid. Our case differs in this respect as avoidance of exposure to *Anisakis* proved less effective than avoidance of ingestion. Nevertheless, in August 2013, our patient experienced generalized urticaria and dyspnea after eating toast that had been prepared on a griddle contaminated with fish. She had been instructed in the use of epinephrine as needed. This accidental dietary transgression would explain the small increase observed in serum specific IgE against *Anisakis*, breaking the sequential decrease observed in figures over time (Table).

We have presented an exceptional case of anaphylaxis due to nonoccupational airborne exposure to *Anisakis* in a patient who was shown to have good tolerance to different fish and shellfish in several oral food challenge tests conducted under anti-*Anisakis* conditions. To our knowledge, this is the first report of nonoccupational airborne-induced anaphylaxis caused by *Anisakis*.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

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Personality Traits May Influence the Severity of Atopic Dermatitis in Adult Patients: A Pilot Study

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Atopic dermatitis (AD) is a recurring inflammatory skin disease that tends to be more severe when it persists into adulthood, with a considerable impact on the quality of life of patients and their families [1]. Its pathogenesis is complex and involves skin barrier impairment and innate and T_H2-driven immunological deregulation [1]. Psychological factors may play a pivotal role in the manifestations of AD, since symptoms of distress potentiate the release of pruritogenic neuromediators and trigger skin inflammation [2]. Personality traits, defined as the way an individual thinks, feels, and behaves, modulate the way patients minimize or tolerate stress or conflicts (coping strategies) [3]. A previous meta-analysis in other chronic diseases found an association between higher scores for personality traits (eg, extraversion, conscientiousness, and openness) and more engagement coping, in contrast with higher scores on neuroticism, which indicate a tendency toward inadequate disease management [4]. In parallel, patients with chronic skin diseases such as psoriasis and AD seem to have distinct personality profiles [5]. In the case of AD, it is not known whether personality traits influence disease severity in a real-life setting.

In this pilot study, we assessed the relationship between the 5 main domains of personality traits and the objective severity of AD in adult patients with chronic disease.

We performed a cross-sectional analysis of patients aged >16 years with a medical diagnosis of AD according to the criteria of Hanifin and Rajka. Patients attending hospital visits were invited to participate. The severity of AD was assessed using the SCORing Atopic Dermatitis (SCORAD) index (0-103), and personality traits were assessed using the short version of the NEO Personality Inventory (NEO-PI-R) [6], which has been validated in the Portuguese population [7]. NEO-PI-R is a 60-item multiple-choice questionnaire used to evaluate the 5 main dimensions of personality: neuroticism (measure of emotional stability), openness (predisposition

to new experiences), extraversion (the main energy focus being held in- or outwards), agreeableness (the ability to deal with others), and conscientiousness (the sense of right and wrong with respect to one's own behaviour). The local ethics committee approved the study, and all the participants gave their informed consent. Participants with severe skin disease other than AD, secondary infection (bacterial, fungal, or viral), or any major systemic disease were excluded. Sample size calculations were performed to determine the number of participants needed to detect effect sizes based on minimal clinically important differences in the SCORAD index: 42 patients were needed to detect a difference with a 2-tailed .05 significance level and a probability of 81% if the true difference in SCORAD between groups was 8.7 units. Of the 78 patients invited, 46 agreed to participate during hospital visits. Two were excluded because of significant comorbidities (diabetes mellitus type 1 and multiple sclerosis). The data analyzed were from 44 patients (mean age, 30 [13] years; 61% female; 77% atopic) who had had AD for a mean of 16 (10) years. Eleven patients (25%) had mild AD, 18 (41%) moderate AD, and 15 (34%) severe AD. The mean SCORAD was 44.9 (27.3). A 1-way ANOVA was applied, and a post hoc Bonferroni correction was performed when significant differences were detected.

We found that participants scoring high on conscientiousness had less severe disease than those scoring normal (mean [95%CI] SCORAD of 31.17 [19.58-42.58] vs 56.16 [42.73-68.67]; P=.039). No further differences were observed for neuroticism (P=.960), extraversion (P=.065), openness (P=.722), or agreeableness (P=.186) (Table).

The fact that personality traits can affect the severity of AD is a key finding of our study. In contrast with results from a previous experimental setting [8], we found that higher conscientiousness was associated with less severe disease. Conscientiousness is associated with being methodical, hardworking, efficient, and organized and focused on solving tasks effectively in a results-oriented fashion [3]. It has also been associated with a consistent protective effect, predicting lower risk for internalizing problems [4]. We hypothesize that this personality trait can enhance adherence to treatment and diminish the impact of stressful stimuli. We also observed that patients scoring simultaneously low in extraversion and high in neuroticism tended to have higher mean SCORAD values (data not shown), probably because of emotional instability dominated by vulnerability to experiences of anxiety and general distress.

Our study is subject to a series of limitations. First, its cross-sectional design prevents us from assessing the causal directionality of the associations. Second, the sample was small. Although the sample size was similar to that of previous studies [9,10] and we managed to include an adequate number of patients according to our sample size calculation, we cannot exclude the possibility that the number of patients within each category was insufficient to generate statistically significant results. Third, although SCORAD is highly recommended as a measure of disease severity in clinical studies owing to its validation and reproducibility, it has the disadvantage of being dependent on the examiner's subjectivity. However, all the patients were evaluated by the same trained investigator to minimize this effect. Finally, the natural course of AD, which is characterized by remissions and flares, makes it more difficult to evaluate the cross-sectional

Table. Personality Traits and Severity of Atopic Dermatitis

Personality Trait	Category	No. (%) of Patients	SCORAD		
			Mean	95%CI	P Value[a]
Neuroticism	Low	9 (20)	47.21	22.23-71.66	
	Normal	21 (48)	45.22	32.54-57.27	.960
	High	14 (32)	44.23	28.39-58.61	
Extraversion	Low	2 (5)	83.12	−190.68 to 355.68	
	Normal	18 (40)	37.14	24.95-49.72	.065
	High	24 (55)	47.16	36.05-58.70	
Openness	Low	3 (7)	42.21	−10.79 to 95.46	
	Normal	25 (57)	48.43	35.03-60.57	.722
	High	16 (36)	41.32	28.51-52.79	
Agreeableness	Low	13 (30)	55.13	38.07-72.55	
	Normal	20 (46)	38.31	27.65-48.93	.186
	High	12 (24)	48.12	20.96-75.04	
Conscientiousness	Low	12 (27)	41.13	22.43-58.74	
	Normal	20 (45)	56.16	42.73-68.67	.035
	High	12 (28)	31.17	19.58-42.58	

Abbreviations: SCORAD, SCORing Atopic Dermatitis.
[a]One-way ANOVA. Patients scoring very low and low or very high and high were grouped into low and high, respectively

relationship between disease severity and personality traits, which are structural characteristics.

Our study also has notable strengths. It was carried out in an outpatient setting with validated clinical outcomes, as previously suggested by other authors [8]. We applied the same psychological questionnaires that had been used in a recent European multicenter survey [10] and that were previously validated in the Portuguese population, thus facilitating future comparisons. Furthermore, ours is the first study to explore the relationship between personality traits and severity of AD in a clinical setting.

We conclude that personality traits can influence the severity of AD in adult patients with long-term disease. Longitudinal studies addressing the role of personality in attaining control of AD are needed to draw definitive conclusions. Psychological assessment and training in adaptive coping strategies to enhance self-control may benefit patients with chronic AD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Anaphylactic Shock Caused by a Hidden Allergen in Blood Sausage

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A 47-year-old woman was treated for anaphylactic shock in the emergency room. Upon waking, she experienced vomiting, diarrhea, severe itching on the palms and soles that became generalized, as well as erythema and wheezing dyspnea. The physical examination in the emergency room revealed low blood pressure (76/52 mmHg), tachycardia, and hypophonesis. Treatment with intramuscular adrenaline, antihistamine, and intravenous corticosteroids led to a full recovery. The patient was referred to our allergy department. Her medical history revealed surgery for a pituitary microadenoma 15 years earlier. She had been diagnosed with allergic rhinoconjunctivitis induced by house dust mites and pollen and allergic asthma induced by dog epithelium 10 years earlier. In the 5 years preceding her visit, she had only experienced asthma symptoms occasionally when exposed to dogs. She reported itching of the mouth when eating pistachios.

Onset of anaphylactic shock was 4 hours after eating scrambled eggs, blood sausage, and tuna dumplings with tomato sauce for dinner. Nonallergic anaphylaxis was ruled out. After thorough questioning, drugs, physical exercise, and alcohol were ruled out as cofactors in this episode. Other causes of anaphylaxis such as drugs, gastroallergic anisakiasis, hydatid disease, and mastocytosis were excluded. Serum tryptase levels measured several weeks after the anaphylactic reaction were within the normal range (5.6 μg/L). Pheochromocytoma and carcinoid syndrome were also ruled out.

The ingredients listed on the blood sausage label were pork jowl, bacon, onion, pig's blood, and spices. The manufacturer provided us with a list of the spices (caraway, black pepper, paprika, cinnamon, nutmeg, clove, coriander, and marjoram). The results of skin prick tests (SPT) were positive to mugwort pollen (with a mean wheal diameter of 9 mm), *Cupressus arizonica* pollen (5 mm), *Lolium perenne* pollen (6 mm), pine nut, pistachio, and cat and dog dander. The results were negative for cereal flours, peach lipid transfer protein (LTP), egg, *Anisakis* species, oregano, cinnamon, onion, mustard, paprika, black pepper, nutmeg, lupine, and coriander. SPT results using our in-house spice extracts (10 mg/mL in phosphate-buffered saline) were positive for caraway (4 mm),

coriander (3 mm), green aniseed (3 mm), cumin (3 mm), fennel (4 mm), histamine control (6 mm), and negative control (0 mm). Prick-by-prick tests were positive to caraway (3 mm) and negative to egg, raw and fried blood sausage, tomato sauce (all from the same brands as those consumed by the patient), cumin, clove, aniseed, and coriander. The results of SPT performed with all of the aforementioned extracts were negative in 5 nonatopic controls and in 5 atopic patients.

Total IgE was 47.90 kU/L. Specific IgE measurements (ImmunoCAP, Thermo Fisher) were positive for *C arizonica, L perenne*, mugwort pollen (2.4 kU$_A$/L), and dog and cat dander. Measurements were negative to dog, cat, and bovine and porcine serum albumins. Determination of specific IgE (ImmunoCAP) to celery, aniseed, coriander, fennel, and caraway was negative in 2 tests. Specific IgE measurements using microarrayed allergens (ISAC, Thermo Fisher) indicated positive results (medium-high) to mugwort LTP, nArt v3 (1 ISU), nArt v 1 (2.2 ISU), grass pollen group 1, major allergens from *C arizonica*, rFel d 1, and rCan f 1. Determination of specific IgE to ω-5 gliadin (rTri a 19), animal serum albumins, and the remaining allergens was negative. The patient later tolerated pig meat, onion, eggs, blood sausage without spices, lamb, and beef.

Allergenic proteins in caraway, coriander, and blood sausage were studied using IgE-immunoblotting and immunoblot-inhibition assays. Of the several allergenic bands observed, an IgE-binding band at 22 kDa was prominent (Figure). IgE binding was not observed when the allergens were incubated with a control serum. Immunoblotting-inhibition showed that IgE binding to caraway extract was inhibited when the patient's serum was preincubated with blood sausage and vice versa.

The patient was diagnosed with anaphylactic shock caused by caraway and coriander contained in blood sausage and sensitization to other spices from the Apiaceae family. Subsequently, spices from this family were eliminated from her diet, and she has had no further anaphylactic reactions in the 5 years since then.

We report a case of anaphylactic shock in a pollen-allergic patient caused by a hidden allergen, caraway, which was not included in the list of ingredients on the product label. The strong SPT positivity for mugwort pollen and the postprandial
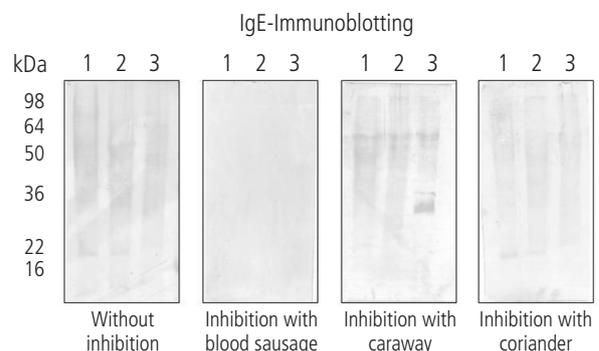

Figure. IgE-immunoblotting and immunoblotting-inhibition assays. Patient's serum incubated with extracts from blood sausage (lane 1), caraway (lane 2), and coriander (lane 3).

systemic reaction raised clinical suspicion of a reaction to the spices [1] and aided us in our diagnosis despite the weak SPT positivity for known spices and the negative results of specific IgE determinations using ImmunoCAP. However, the patient was sensitized to mugwort LTP, a thermostable protein that is resistant to digestion and responsible for severe reactions. Blood sausage and caraway IgE immunoblots and immunoblot-inhibition showed several allergenic bands, especially the 22-kDa allergen. Previous studies on spices from the Apiaceae family revealed allergenic components of 60 kDa [2,3] and of 12 and 14 kDa [3]. A homologous Bet v 1 allergen and a profilin-related allergen have also been identified in several spices [2], and an LTP has been detected in fennel [4], parsley [5], and saffron [6]. To our knowledge, caraway allergens have not been previously identified.

Allergy to spices is uncommon, accounting for 2% of all food allergies and 6.4% of food allergies in adults [1]. Young adults sensitized to mugwort and birch are at risk of spice allergy [1]. Spices from the Apiaceae and Umbelliferae families, particularly aniseed, coriander, caraway, and celery, can induce severe allergic systemic reactions. Small amounts of proteins are able to produce a reaction.

Extensive allergenic cross-reactivity between species from the Apiaceae family is common. Cross-reactivity between food spices belonging to the Umbelliferae family and pollens from the Compositae family has been reported [7]. Celery-mugwort-spice syndrome is a well-known example of pollen cross-reactivity with spices [8,9]. However, our patient was not sensitized to celery. Allergy to serum albumins from animals, which contain proteins that are allergens in various mammalian products, was also ruled out.

In pollen-allergic patients who are sensitized to mugwort, the role of spices in food allergies should be assessed, especially in postprandial reactions [1], bearing in mind that they may be hidden allergens. We present a case of anaphylaxis to blood sausage in which caraway allergens were hidden. Caraway allergens have not been isolated to date, and further studies are necessary to better characterize them.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Sensitization to Minor Allergens Has a Direct Influence on the Outcome of Subcutaneous Immunotherapy in Olive-Allergic Patients

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Olive pollen is a significant and complex source of allergens in southern Europe [1-2]. A study of 891 patients showed that, in areas with high olive pollen exposure, olive-allergic patients present not only specific IgE (sIgE) to a major olive allergen (Ole e 1), but also significant levels of sIgE to minor allergens such as Ole e 7 and Ole e 9 [3]. One publication established an association between sensitization to these minor allergens and poor tolerance to specific immunotherapy, with patients sensitized to Ole e 7 or 9 showing a 2-fold greater risk of asthmatic symptoms than patients sensitized only to Ole e 1 [4]. Our objective was to determine how sensitization profile affects the outcome of immunotherapy, which, in terms of immune changes and effectiveness, is analyzed according to the patients' sensitization profile, namely, whether patients are sensitized to Ole e 1 only or to Ole e 1 and Ole e 7 and/or Ole e 9.

This noninterventional, open-label, parallel-group study was carried out with the approval of the local ethics committee. Written informed consent was obtained from all participants. The study population comprised 76 patients, who were included consecutively before the pollen season (20 monosensitized to Ole e 1 [Oe1 group] and 56 sensitized to Ole e 1 and Ole e 7 and/or Ole e 9 [Oe79 group]).

The inclusion criteria were age 5 to 55 years with a ≥2-year clinical history of troublesome symptoms of allergic rhinoconjunctivitis with/without asthma symptoms during the olive pollen season and a positive result in skin testing and determination of sIgE to *Olea europaea* (ImmunoCAP, Thermo Fisher, ≥0.35kU$_A$/L).

All patients received subcutaneous immunotherapy (SCIT) with a depot extract (Pangramin Plus *Olea europaea*, ALK-Abelló, SA). The Ole e 1 content was 15 µg/mL; that of Ole e 9 and Ole e 7 was 0.5 µg/mL. The build-up phase comprised a cluster schedule of 4 weekly visits and 2 doses/visit.

The level of sIgE to the different allergens was tested using the ADVIA Centaur platform (Bayer HealthCare, Diagnostics Division) [5], which has previously been used in epidemiological studies [3]. Specific IgG4 (sIgG4) against Ole e 1, Ole e 9, and Ole e 7 was determined using ELISA.

sIgE and sIgG4 were measured at T0 (baseline), T1 (updosing completed), and at T2 and T3 (6 and 18 months of treatment). Nasal, ocular, and bronchial allergic symptoms and the use of rescue medication (a very simple protocol comprising loratadine and Symbicort as needed) were recorded daily for 4 weeks during 2 consecutive olive pollen seasons. Symptoms were graded from 0 to 3 according to severity. Loratadine was given 1 point/tablet and Symbicort 2 points/puff. Symptom and medication scores were calculated.

Adverse reactions to SCIT were recorded in accordance with the European Academy of Allergy and Clinical Immunology (EAACI) classification [6].

The demographic characteristics of both groups (Oe1 vs Oe79) were similar in terms of age and sex. Seventy percent of the patients in the Oe1 group had rhinitis with asthma and 30% rhinitis only; in the Oe79 group these percentages were 96.2% and 3.8%, respectively (P=.0042). The time since the onset of symptoms of the allergic disease was similar in both groups (P=.3356).

The Table shows the changes in sIgE and sIgG4 to Ole e 1, 7, and 9 in both groups at T1, T2, and T3 compared with T0.

When the correlation between increases in sIgE and increases in sIgG4 was analyzed for the 3 allergens, it was only statistically significant for Ole e 1 at T3 (r^2=0.51, P<.0001). The correlation was significant at T0, T2, and T3 for Ole e 7 (r^2=0.80, P<.0001; r^2=0.81, P<.0001; and r^2=0.77, P<.0001) and for Ole e 9 (r^2=0.62, P<.0001; r^2=0.82, P<.0001; and r^2=0.86, P<.0001).

No statistical differences were found between the 2 groups for the symptom score at T2 or T3. In the case of the medication score, the Oe1 group needed less antiasthmatic medication than the Oe79 group at T2 (P=.0184) and at T3 (P=.0091).

Systemic reactions were more frequent in the Oe79 group. In the Oe1 group, 16 reactions were recorded in 5 patients (all mild, delayed, grade I [EAACI]); in the Oe79 group, 35 reactions (31 grade I, 3 grade II, and 1 grade III, 75% delayed) were recorded in 28 patients. No serious adverse reactions were recorded, and no patients discontinued treatment owing to adverse reactions.

Given that more than 1 sensitization pattern is often observed in areas with an extended high allergen burden [7], Ole e 7 and Ole e 9 become major allergens. Component-resolved diagnosis enables individual sensitization and a better therapeutic approach for polysensitized patients [8-9]. The sIgE values for the components studied were always consistent with the kinetics observed in SCIT (initial elevation and subsequent decrease) [10] in each group, and IgG4 tended to behave as expected. Of note, in the Oe79 group, sensitization to Ole e 9 was always consistent with sensitization to Ole e 1, as were the changes associated with this sensitization. However, this was not the case for Ole e 7.

The different sizes of the 2 subgroups are indicative of the population in a region with an extremely high concentration of olive pollen, in which Ole e 7 and Ole e 9 are major allergens associated with a high prevalence of asthma.

The present study could be considered a pilot study that demonstrated more than 1 form of olive pollen allergy. The consequences for routine clinical practice are the need to identify sensitization to minor allergens in areas with a

Table. sIgE and sIgG4 to Ole e 1, Ole e 7, and Ole e 9

	Visit	No.	Median	95% CI, Lower Limit	95% CI, Upper Limit	P Value[a]
Group Oe1						
IgE Ole e 1, kU$_A$/L	T1 vs T0	20	4.35	1.48	14.54	.0003
	T2 vs T0	19	5.02	3.51	20.33	<.0001
	T3 vs T0	18	1.61	−7.53	18.11	.1415
IgG4 Ole e 1, mg/L	T1 vs T0	20	0.22	0.12	0.42	<.0001
	T2 vs T0	19	0.43	0.27	0.83	<.0001
	T3 vs T0	18	0.93	0.54	1.78	<.0001
IgE Ole e 7, kU$_A$/L	T1 vs T0	20	0.01	−0.04	0.47	.0256
	T2 vs T0	19	0.04	−0.04	1.72	.0076
	T3 vs T0	18	0.28	1.41	9.16	.0005
IgG4 Ole e 7, mg/L	T1 vs T0	20	0	−0.01	0.18	.0195
	T2 vs T0	19	0	−0.08	0.4	.0068
	T3 vs T0	18	0.02	0.14	1.49	.0002
IgE Ole e 9, kU$_A$/L	T1 vs T0	20	0.01	−0.33	1.09	.1327
	T2 vs T0	19	0.01	−0.62	2.66	.0728
	T3 vs T0	18	0.02	0.07	7.3	.1297
IgG4 Ole e 9, mg/L	T1 vs T0	20	0	−0.01	0.03	.7500
	T2 vs T0	19	0	0	0.03	.0625
	T3 vs T0	18	0.01	−0.01	0.21	.0039
Group Oe79						
IgE Ole e 1, kU$_A$/L	T1 vs T0	53	1.79	−2.99	11.49	.0007
	T2 vs T0	52	5.41	1.58	19.85	<.0001
	T3 vs T0	53	0.6	−5.61	6.81	.5376
IgG4 Ole e 1, mg/L	T1 vs T0	53	0.16	0.15	0.37	<.0001
	T2 vs T0	52	0.39	0.37	0.72	<.0001
	T3 vs T0	53	0.75	0.61	1.27	<.0001
IgE Ole e 7, kU$_A$/L	T1 vs T0	53	1.18	5.32	16.54	<.0001
	T2 vs T0	52	10.09	10.32	22.31	<.0001
	T3 vs T0	53	6.21	5.11	17.45	<.0001
IgG4 Ole e 7, mg/L	T1 vs T0	52	0.61	0.66	1.61	<.0001
	T2 vs T0	52	0.96	0.73	2.38	<.0001
	T3 vs T0	52	1.98	1.87	4.4	<.0001
IgE Ole e 9, kU$_A$/L	T1 vs T0	53	2.26	6.17	18.72	<.0001
	T2 vs T0	52	4.42	7.76	23.03	<.0001
	T3 vs T0	53	0.22	−0.92	12	.0119
IgG4 Ole e 9, mg/L	T1 vs T0	53	0.09	0.12	0.44	<.0001
	T2 vs T0	52	0.02	0.11	0.28	<.0001
	T3 vs T0	53	0.19	0.29	0.67	<.0001

[a]Wilcoxon signed rank test.

high environmental concentration and the need to choose immunotherapy extracts with a controlled and uniform content in terms of Ole e 1, Ole e 7, and Ole e 9.

Appropriately designed studies are required to determine the short- and long-term clinical response parameters in the different sensitization groups.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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The Smartphone: A Novel Diagnostic Tool in Pollen Allergy?

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The diagnosis of pollen-induced allergic rhinitis (AR) is based on a thorough clinical history confirmed by positive results in testing with aeroallergens. Tests can be in vivo (skin prick test [SPT]) and in vitro (assays for determination of IgE). The pollination season of the triggering allergens must coincide with the period during which the patient has the respiratory symptoms [1,2]. In allergy epidemics, however, most AR patients are sensitized to multiple aeroallergens. The etiological diagnosis of seasonal AR is therefore difficult, especially in geographic areas such as the Mediterranean, where many pollens have an overlapping pollination season. Component-resolved diagnosis is a molecular-based approach that can discriminate between sensitization to species-specific, genuine allergenic molecules and sensitization to highly cross-reactive molecules (eg, profilins, polcalcins, and pathogenesis-related 10 proteins) shared by various types of pollen [3]. Nonetheless, it cannot identify the trigger in patients sensitized to species-specific molecules of pollens with overlapping pollination periods.

The use of smartphones and electronic clinical diaries has introduced new possibilities for monitoring chronic diseases [4] such as hypertension, diabetes [5], and asthma [6]. In particular, web-based management of asthmatic patients is feasible, safe, and preferred by patients [6]. The use of smartphones has also become more common in allergology, and patient-centered systems have recently been developed to fill gaps in disease management by using information and communications technology tools and a clinical decision support system [7]. During the last few years, we have accumulated experience from the application of mobile health (mHealth) technology to monitor adherence to treatment of children with allergic rhinitis [8,9]. While mHealth is already being investigated as a monitoring tool, there are, to our knowledge, no reports in the literature indicating that it can assist in the diagnosis of AR.

We report on 2 patients who were sensitized to multiple seasonal allergens with overlapping pollination periods and to whom a diagnostic solution was offered in the form of an mHealth monitoring app. The patients were asked to register their symptoms daily during May and June 2011 using a smartphone with a dedicated electronic clinical diary app (AllergyMonitor, TPS Production). This app records disease severity and symptom scores (eg, the Rhinoconjunctivitis Total Symptom Score [RTSS]) and enables them to be compared against locally relevant pollen counts. The patients and their parents were instructed in the use of the app by a pediatrician (AB), who spent about 10 minutes per patient on instruction. The data were entered into the app directly by the children, who were assisted by their parents. The pediatrician, however, had no direct control over this daily activity.

The patients were a 10 year-old boy and a 7-year-old boy, both of whom had had persistent moderate-severe AR from the age of 3 years. The children had been living in Ascoli Piceno, Marche, Italy since birth and reported having had rhinitis symptoms (stuffy, runny, and itchy nose with sneezing) for the previous 2 years, mainly during May and June. The results of SPTs with allergenic extracts (ALK-Abelló, Denmark) were positive (wheal diameter ≥3 mm) in both cases for many pollens, including olive and timothy grass (Figure, A and B), whose pollination period in Ascoli Piceno is between April and June. Component-resolved diagnosis (UniCAP, TFS) performed using sera provided evidence of cosensitization (cutoff ≥0.35 kU$_A$/L) not only to the major allergenic molecules of olive (Ole e 1), timothy grass (Phl p 1, Phl p 5), and—in the first patient—pellitory (Par j 2), but also to cross-reacting molecules (Phl p 12, profilin; Phl p 7, polcalcin) (Figure, A and B). The pediatrician was unable to tailor therapy based on these data. Comparing the RTSS and the pollen counts on the app, the peak of the symptoms for the first patient coincided with the peak of the olive pollen counts (Figure, A), while for the second patient it coincided with peak grass pollen counts (Figure, B). Based on these data, the pediatrician was able to prescribe immunotherapy against olive pollen allergens in the first patient and grass pollen allergens in the second one.

Both cases present similar diagnostic challenges; no clear-cut decision could be reached using the traditional allergological evaluation with SPT or using the innovative molecular approach of determination of IgE against genuine and cross-reacting allergenic molecules. However, the prospective and consistent recording of nasal and conjunctival symptoms during the pollination season played a key role in the identification of the trigger pollen (olive pollen in the first case, grass pollen in the second). To our knowledge, this is the first report of an etiological diagnosis of pollen allergy substantiated by a smartphone app. Comparison between the RTSS and pollen curves can guide the physician when deciding on immunotherapy. The inclusion of medication use in the registration is important. The app AllergyMonitor enables the patient to record medication intake and calculates several symptom and medication scores (Florack et al, submitted).

Our report is subject to a series of limitations. First, our findings are based on 2 cases only, although larger studies are being planned to test the hypotheses generated here. Second, the patients' symptoms were monitored in 1 pollen
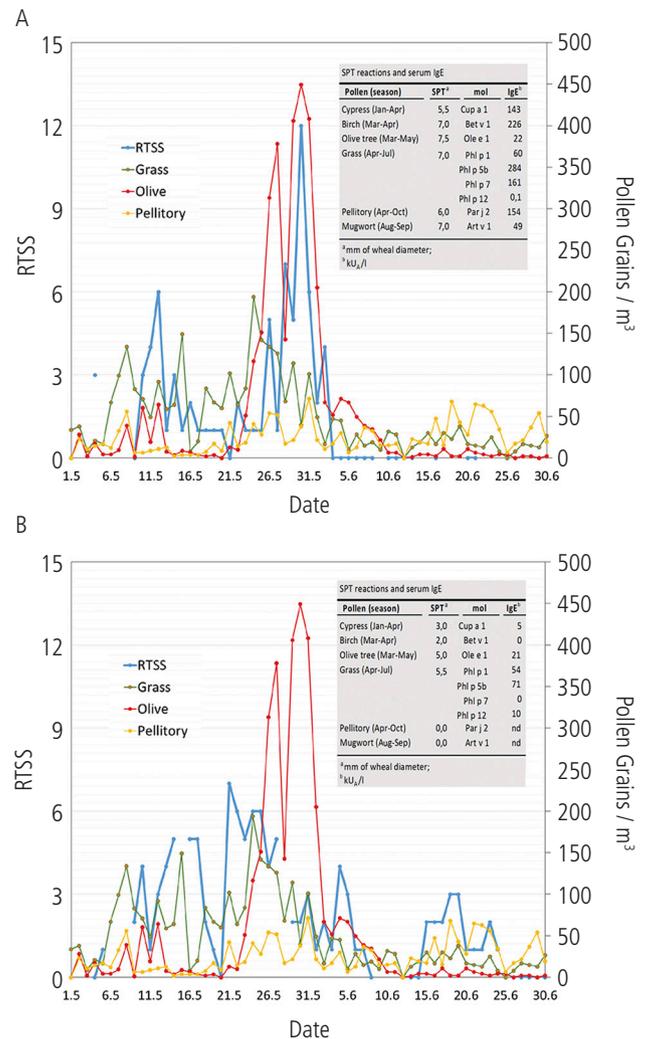

Figure. Symptom severity vs pollen counts in 2 patients with allergic rhinitis. Data on severity of symptoms (collected using a smartphone app) are reported as the Rhinoconjunctivitis Total Symptom Score (RTSS) (A, Patient 1; B, Patient 2). Pollen counts (grains/m³) were obtained from the pollen station of Ascoli Piceno. Data on skin prick test reactions to pollen extracts and on serum IgE levels against major allergenic molecules are shown. We also measured the following serum IgE levels (kU$_A$/L) against pollen extracts: Patient 1, cypress 143, birch 226, olive tree 122, grass 404, pellitory 191, mugwort 96; Patient 2, cypress 2, birch 9, olive tree 24, grass 157.

season only; longer follow-up covering consecutive springs is necessary. Third, some of the second patient's values were missing, although a statistical analysis performed after linear interpolation of the data confirmed the conclusions obtained before interpolation (findings not shown).

In conclusion, mHealth technology is increasingly used and has many potential benefits: a more precise clinical history, prospective recording of objective patient parameters, support for diagnostic and clinical decisions, better doctor-patient and doctor-doctor communication, monitoring of the safety of treatment and adherence, facilitation of implementation of guidelines, patient education and awareness, and reduced

costs [4-9]. Our findings suggest that this novel, noninvasive diagnostic tool warrants further investigation in order to verify its usefulness and potential in the clinical diagnosis of pollen-allergic patients.

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Oral Immunotherapy for Management of Peanut Allergy in Spanish Children

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In Spain, nuts and fruits are the main cause of food allergy in children aged >5 years [1]. Allergy to peanuts is the most common cause of fatal and near-fatal allergic reactions to foods and seems to be lifelong, since only 20% of allergic children outgrow it [2].

Oral immunotherapy (OIT) is a new approach in the management of food-allergic patients. It is based on the administration of small amounts of allergen that are gradually increased with the aim of inducing desensitization as a first step toward achieving tolerance [3].

Table. Protocol for Oral Immunotherapy With Peanut

Induction phase: doses were administered at the hospital. The starting dose was adjusted for each patient according to the dose that elicited allergic manifestations during the open food challenge.

Week	Roasted Peanuts, g
1[a]	0.025-0.05-0.1
2	0.2
3	0.4
4	1
5	1.5
6	3
7	5

[a]The starting dose was established by open food challenge and set at the dose preceding the dose that elicited symptoms.
Initially, dry roasted peanuts were ground and mixed with yogurt. When 1 g was reached, peanuts were administered as is.
Oral disodium cromoglycate (100 mg every 8 hours) was administered during this phase.

Maintenance phase: doses were administered at home

5 g of roasted peanut daily for 3 months.

5 g 2-3 times a week afterwards.

Most studies on OIT with peanut have been performed in the United Kingdom and the United States of America, where peanut allergy is considered a matter of public health. Although peanut allergy is less prevalent in Spain than in the United States of America, patients are mostly sensitized to the lipid transfer protein (LTP) Ara h 9, which is associated with severe systemic reactions [4].

Using OIT we aimed to reach an amount of peanut that was sufficient to avoid severe adverse reactions in case of accidental exposure. Our OIT protocol is summarized in the Table. Informed consent was obtained from each family before the protocol was started.

The first patient was a 5-year-old girl with atopic dermatitis (AD) and rhinitis who was sensitized to dust mites. At 4 years of age she developed generalized urticaria, vomiting, and abdominal pain after ingestion of roasted peanuts. The result of a skin prick test (SPT) with peanut extract (ALK-Abelló) was positive (12 mm). Total serum IgE was 88.5 kU/L and peanut specific IgE was 14.3 kU_A/L (Thermo Fisher Scientific). We started OIT after establishing an initial dose of 0.025 g by open food challenge (OFC). The induction phase took 9 weeks, during which the patient presented vomiting and oral itching on 2 occasions.

She has been on maintenance treatment for 6 months and has not reported allergic reactions to peanut.

The second patient was a 5-year-old boy with AD, rhinitis, and bronchial asthma who was sensitized to dust mites. At 4 years of age, he developed contact urticaria after touching roasted peanuts. SPT with 1 peanut (ALK-Abelló) was positive (11 mm). During OFC with roasted peanuts he developed oral itching and perioral urticaria after ingestion of 0.1 g. OIT was started with an initial dose of 0.05 g. The induction phase took 10 weeks, and during this time, he presented a rash on his chest on 1 occasion.

At the beginning of the maintenance phase, the patient developed abdominal pain after inadvertently ingesting 10 g of peanut. From that moment on, he refused to eat peanuts and therefore did not keep up with his recommended daily intake, eating peanuts only now and then. Two weeks later, during vigorous play after eating peanuts, he developed urticaria on his face and chest that resolved with oral antihistamines and corticosteroids. He subsequently dropped out of the protocol, although he tolerates foods with trace amount of peanuts.

The third patient was a 12-year-old boy with AD, rhinitis, and bronchial asthma who was allergic to kiwi and sensitized to dust mites. He had previously undergone desensitization to egg. At 18 months of age, he developed facial urticaria and angioedema after placing a single peanut in his mouth. The result of SPT to peanut (ALK-Abelló) was positive (8 mm). Total IgE was 175 kU/L and peanut specific IgE was 1.53 kU_A/L (Thermo Fisher Scientific). At 7 years of age, he developed generalized urticaria and difficulty breathing after eating potato chips fried in peanut oil. Two years later, he developed urticaria on his face and chest after ingesting 0.5 g of peanut during an OFC. OIT was started with an initial dose of 0.025 g. The induction phase took 10 weeks, during which time he developed oral itching on 2 occasions. He has been on maintenance treatment for the last 3 years and has not reported adverse reactions.

The fourth patient was a 13-year-old girl with AD, rhinitis, and bronchial asthma who was sensitized to dust mites and *Alternaria alternata*. When she was 3 years old, she developed facial urticaria and oral pruritus after ingestion of 1 peanut. The result of SPT was positive (6 mm) for peanut (ALK-Abelló). Total IgE was 534 kU/L and peanut specific IgE was 2 kU_A/L (Thermo Fisher Scientific). OFC performed at age 11 years confirmed persistence of peanut allergy. The patient started OIT at an initial dose of 0.1 g. The induction phase took 9 weeks, during which time she complained of mild oral itching on 5 occasions that resolved spontaneously.

She has not reported adverse reactions during the last 2 years of the maintenance phase.

Most studies on OIT to peanut show that a high percentage of patients achieve complete desensitization [5-7]. Moreover, reports of immunological changes [5-7] suggest that OIT modulates the immune response towards tolerance in peanut-allergic patients. Recently, Syed et al [8] demonstrated epigenetic changes in patients' immune tolerance to peanut after OIT, namely, increased methylation of FOXP3 CpG sites in antigen-induced regulatory T cells.

To date, only 1 patient has undergone OIT for allergy to peanut. The patient was a 6-year-old child who tolerated 5.5 g of peanuts after a 138-day induction phase [9].

Of the 4 patients we present here, 3 achieved the target dose of 5 g of peanut after a 9 to 10–week induction phase and can now tolerate peanut.

Adverse reactions during OIT to peanut are mild and usually affect the skin, gastrointestinal tract, and upper respiratory tract [5-7,9]. The frequency of adverse reactions during the induction phase ranges from 1.2% [5] and 2.6% [6] to 46% [7]. These differences are probably related to the type of protocol applied and the target dose of peanut to be reached. We found that 18% of adverse reactions were related to the doses administered during the induction phase. Oral itching was the most frequent adverse reaction reported. Two mild reactions were observed in only 1 patient during the maintenance phase.

Patients on maintenance treatment and their families reported an improvement in quality of life in terms of allergen avoidance, risk of accidental exposure, and limitations at social occasions such as birthday parties. This issue has been assessed by Anagnostou et al [10] and constitutes another factor that tips the scale in favor of OIT.

Based on our limited experience and that of other authors, OIT to treat peanut allergy seems to be a safe procedure that elicits mild adverse reactions and improves quality of life for both patients and their families.

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Asthma and Allergic Diseases in a Selected Group of Patients With Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) is the most common symptomatic primary immune deficiency. It is characterized by decreased serum Ig concentrations of at least 2 isotypes in patients older than 4 years with confirmed specific antibody deficiency against protein and polysaccharide antigens [1]. Although several genetic defects have been identified in the pathogenesis of CVID [2], the basic molecular defect remains unknown. The main clinical manifestations in CVID patients are recurrent infections of the respiratory and gastrointestinal tracts, autoimmune disorders, enteropathy, and lymphoproliferative diseases [1]. Furthermore, mucosal immunodeficiency in patients with CVID could predispose to development of allergic reactions to aeroallergens, inflammation, and bronchial hyperresponsiveness, as reported in IgA deficiency [3]. However, little evidence is available on the prevalence of asthma and allergic diseases in patients with CVID. The purpose of the present study was to report the prevalence of asthma and allergic disease in patients with CVID and to evaluate the association between asthma and allergic diseases and clinical and immunological data from patients attended at our center.

We analyzed data on asthma and allergic diseases, clinical manifestations, and immunological findings from 187 patients (112 males and 75 females) referred to the Children's Medical Center, Pediatrics Center of Excellence, which is affiliated with the Tehran University of Medical Sciences, Tehran, Iran. Food allergy was defined as a convincing history of food allergy and/or self-reporting of a physician-diagnosed food allergy. The inhalant allergens were trees (elm, maple, oak), grasses (Bermuda grass, Johnson grass, June grass

[Kentucky bluegrass]), weeds (common ragweed, cocklebur, rough pigweed), molds, and miscellaneous allergens (mite, dog dander, cat dander, cockroach). CVID patients were divided into 2 groups: CVID patients with asthma and allergic diseases (Group A) and CVID patients without asthma and allergic diseases (Group B).

Clinical and immunological data are presented in the Table. Of the 187 patients, 22 (11.7%) had asthma and allergic diseases, and 7 (3.7%) presented more than 1 allergic manifestation. Only 5 individuals had been referred with allergic complications as their first manifestation before diagnosis of CVID. Twenty patients (10.6%) had at least 1 first-degree relative with allergic manifestations. The prevalence of asthma and allergic disorders in CVID patients are presented in the Table.

The mean (SD) serum level of IgM at diagnosis was significantly lower in Group A than in Group B (29.0 [21.9] vs 44.2 [6.2] mg/dL; P=.03), whereas the level of IgE was significantly higher (median, 41.62 IU/mL vs 30.18 IU/mL; P=.04). Significant differences between Group A and Group B were observed for anti-IgA antibody level (5.06 [3.3] vs 1.6 [1.0] IU/mL; P=.02) and IgE after stimulation (6.13 [5.5] vs 3.17 [2.8] IU/mL; P=.01). Furthermore, a comparison of the clinical complications between the 2 groups revealed significantly more frequent upper respiratory tract infections (8.3 [7.4] vs 5.8 [4.7]; P=.001) and bronchiectasis (50% vs 26%; P=.003) in Group A than in Group B.

The prevalence of asthma and allergic disorders in patients with CVID reported elsewhere [4-6] was higher than that found in our study (12%). This discrepancy could be due to the difference in sample size, underlying genetic defects, and ethnic composition. Moreover, as our patients were predominantly Caucasian, our findings cannot be applied to other ethnic groups. Asthma and other atopic diseases in patients with CVID can be caused by immune dysregulation, association with some specific major histocompatibility complex haplotypes, reduced IgA response to luminal allergen challenge, increased levels of serum IgE due to a compensatory mechanism for reducing other Ig classes, and prolonged respiratory infections. Consistent with other studies, we found that few patients had allergic rhinitis (1%) [4,5]. However, Eguíluz-Gracia et al [6] and Agondi et al [7] found a greater prevalence of allergic rhinitis (35.5% and 43%, respectively). Food and drug allergies were also less frequent than reported elsewhere [4,6,8], whereas urticaria was more frequent [6,9]. Atopic dermatitis affected the same percentage of patients in

Table. Clinical and Immunological Data for 187 Patients With CVID

Parameters	Total (N=187)	Group A (n=22)	Group B (n=165)	P Value[a]
Asthma, %	9 (4.8)	9 (40.9)	-	-
Atopic dermatitis, %	6 (3.2)	6 (27.2)	-	-
Allergic eczema, %	4 (2.1)	4 (18.1)	-	-
Food allergy, %	5 (2.6)	2 patients with allergy to pistachios and 3 patients with allergy to eggplant (22.7)	-	-
Urticaria, %	4 (2.1)	4 chronic, 1 induced by exposure to sunlight (18.1)	-	-
Allergic rhinitis, %	2 (1.0)	2 (9.0)	-	-
Allergic conjunctivitis, %	2 (1.0)	2 (9.0)	-	-
Drug allergy, %	2 (1.0)	2 (9.0)	-	-
Anaphylactic reactions to IVIG, %	1 (0.5)	1 (4.5)	-	-
Dust allergy, %	1 (0.5)	1 (4.5)	-	-
Mean (SD) upper respiratory tract infections per person	6.2 (3.7)	8.3 (7.4)	5.8 (4.7)	.001
Mean (SD) lower respiratory tract infections per person	3.2 (2.4)	3.7 (3.5)	2.7 (1.3)	.43
Bronchiectasis, %	54 (31)	11 (50.0)	43 (26.0)	.03
Mean (SD) IgG, mg/dL	277.1 (214.5)	284.3 (197.6)	278.0 (217.0)	.61
Mean (SD) IgM, mg/dL	42.7 (5.9)	29.0 (21.9)	44.2 (6.2)	.03
Mean (SD) IgA, mg/dL	26.3 (4.2)	20.3 (3.5)	27.5 (4.3)	.65
Mean (SD) IgE, IU/mL	32.1 (6.1)	41.62 (6.3)	30.18 (4.6)	.04
Mean (SD) anti-IgA level, IU/mL	2.4 (1.3)	5.06 (3.3)	1.6 (1.0)	.02
Mean (SD) poststimulation IgE, IU/mL	4.2 (1.0)	6.13 (5.5)	3.17 (2.8)	.01

Abbreviations: CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulin.
[a]P value significant at <.05.

our study (3.2%) as reported by Eguíluz-Gracia et al, although our finding was higher than that reported by Ramírez-Vargas et al (0.4%) [4] and lower than that reported by Tuano et al (4.4%) [8].

A significantly higher IgE titer and significantly lower IgM titer were found in patients with asthma and allergic diseases than in the other patients. Increased IgE in Group A suggests the possibility of atopic diseases resulting from skewed Ig class switching to IgE, as confirmed by the high levels of IgE after stimulation. CVID patients with decreased IgM have been shown to be more susceptible to developing bronchiectasis [10]. We consistently showed that upper respiratory infections and bronchiectasis were significantly more common in Group A than in Group B. Moreover, the significantly higher anti-IgA antibody level in Group A could be associated with anaphylactic reaction to intravenous immunoglobulin.

Although infectious diseases are the most common clinical manifestation in patients with CVID, the result of the present study showed that asthma and allergic diseases were also observed in a significant proportion of patients. The development of asthma and allergic diseases in patients with CVID could be associated with immune dysregulation, skewing of the immune system towards a type 2 helper T-cell phenotype, and prolonged respiratory infections.

Our findings show that asthma and allergic diseases are associated with CVID in some cases. Diagnosing asthma and allergic diseases could improve management and, eventually, the quality of life of patients with CVID. Therefore, immunologists and physicians should be aware of these conditions. Moreover, we suggest that this study could be complemented with patients from other countries. Indeed, a prospective study with a larger number of patients would fully elucidate the association between asthma and allergic diseases and CVID.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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