

# Allergenic Profile of Nasal Polyposis

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## ■ Abstract

**Background:** Nasal polyposis is highly prevalent in the general population. Its exact origin is unknown, although several factors are involved in the etiology and development of this condition. Clinical patterns, a history of atopy, environmental exposure, eosinophil-mediated inflammation, the presence of inflammatory mediators, and sensitization to some allergens indicate that nasal polyposis is associated with allergic phenomena. The aim of this study was to identify the association between nasal polyposis and allergic factors by examining hypersensitivity reactions to common allergens and environmental exposure that could lead to the development of atopy.

**Methods:** We conducted a comparative study of 190 patients with nasal polyposis and 190 healthy individuals. The study included clinical and epidemiological variables, environmental exposure factors, and an allergology workup using skin prick tests with 18 inhaled allergens.

**Results:** A total of 121 patients (63.7%) of the 190 were male; 62.1% had a family history of allergy. The incidence of asthma was 48.9% among the patients and only 2.3% among the controls ( $P < .001$ ). The factor most frequently involved in the patients' symptoms was weather changes (67.4%). Skin prick tests were positive in 63.2% of the patients and 31.1% of the controls. The allergens that most frequently elicited a reaction from the patients in the prick tests were *Dermatophagoides pteronyssinus* (27.7%), *Dermatophagoides farinae* (21.3%), and *Olea europaea* (21.1%). The difference between these results and those of the controls was statistically significant.

**Conclusions:** Patients with nasal polyposis are sensitive to the most common allergens in our environment and exhibit a clear-cut correlation with other allergic factors, as confirmed by personal and family histories, the presence of chronic rhinitis, and the results of in vivo tests.

**Key words:** Allergy. Chronic rhinosinusitis. Common airborne allergens. IgE-mediated phenomena. Nasal polyposis. *Olea europaea*.

## ■ Resumen

**Introducción:** La poliposis nasosinusal es una entidad clínica de alta prevalencia en la población general cuya etiología se desconoce, aunque existen múltiples factores involucrados en su origen y desarrollo. Existen indicios de asociación entre la poliposis y los fenómenos alérgicos debido a diferentes factores, como el cuadro clínico, los antecedentes atópicos, la exposición ambiental, la inflamación eosinofílica, los mediadores inflamatorios y fenómenos de sensibilización a alérgenos. El objetivo del estudio es evaluar la asociación entre los factores alérgicos y la poliposis nasal, examinando las reacciones de hipersensibilidad a alérgenos comunes en nuestro medio y los factores exógenos de exposición que pudieran contribuir al desarrollo de atopia en los pacientes.

**Métodos:** Se ha realizado un estudio comparativo entre 190 pacientes con poliposis nasosinusal y un grupo control de 190 sujetos sanos, analizando variables clínicas, epidemiológicas, factores de exposición ambiental y estudio alergológico mediante prick-tests a un panel de 18 neuroalérgenos.

**Resultados:** Un total de 121 pacientes fueron varones (63,7%). Presentaron antecedentes familiares de alergia un 62,1%. La incidencia de asma bronquial entre los pacientes fue de un 48,9% (93 sujetos) frente al 2,1% de los controles, con diferencias estadísticamente significativas ( $P < 0,001$ ). Los factores que con más frecuencia provocaron síntomas en los pacientes fueron los cambios de clima. Entre los pacientes, los test cutáneos fueron positivos en 120 casos (63,2% del total) frente al 31,1% de los controles. En el grupo de pacientes, los prick-test positivos más frecuentes fueron DTP (27,7%), *Olea europea* (21,1%) y DPF (21,3%), todos ellos con diferencias estadísticamente significativas sobre los controles sanos.

**Conclusiones:** En los pacientes con poliposis nasosinusal de nuestra serie, existe una sensibilización frente a los alérgenos comunes más frecuentes de nuestro medio y una clara relación con otros factores alérgicos, comprobada por los antecedentes personales, familiares, historia clínica de rinitis perenne y resultados de test in vivo.

**Palabras clave:** Alergia. Fenómenos IgE-mediados. Neuroalérgenos comunes. *Olea europaea*. Poliposis nasosinusal. Rinosinusitis crónica.

## Introduction

Nasal polyposis (NP) is a chronic, largely unknown condition with no effective long-term treatment and a tendency to recur, despite the fact that specific pathogenic characteristics have been identified.

This entity is known to be associated with bronchial asthma, intolerance to acetylsalicylic acid, and a number of topical and systemic diseases of different origins. There appears to be a potential relationship between NP and allergy; in fact, the pattern is similar to that of perennial rhinitis, with increased eosinophil counts, specific immunoglobulin (Ig) E to several airborne allergens, presence of cytokines, chemokines, and other inflammatory mediators, and increased expression of adhesion molecules in polyps. Some authors have reported sensitization to various allergens in a substantial proportion of patients as a potential trigger for inflammatory mechanisms [1,2].

The exact origin of NP is unknown. However, a variety of allergic [1,2], infectious, inflammatory, anatomical [3], and genetic [4] factors are known to be involved, as are autonomous dysfunction and ciliary, enzymatic, epithelial, and mucopolysaccharide abnormalities. No single pathogenic factor has been shown to apply to all types of polyps, although the potential mechanisms may converge on a single pathway.

NP is a chronic eosinophil-mediated inflammatory process that is maintained and perpetuated by different elements, chemical mediators, and cells. Eosinophils are associated with allergic inflammation and constitute the dominant cell type in polyps. They are present at increased levels in most patients with NP as a result of the action of the cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL) 5, which function to prolong eosinophil survival [5,6].

Analysis of the supernatant resulting from the lysis and centrifugation of polyps [7] has revealed the presence of increased levels of Ig, particularly IgE. Histamine has been found at increased levels in polyps and neighboring mucosa [8], as have various mediators of arachidonic acid [9], such as leukotriene C4 (LTC4), which is associated with recurrence in polyps. Levels of total IgE, eosinophil cationic protein, IL-4, and IL-8, and eosinophil counts have been shown to be significantly higher in patients with NP than in controls [10]. NP usually presents with increased levels of IL-5 and other cytokines [11], particularly in asthma-related NP [12]. Finally, polyps contain adhesion molecules of the VLA-4 and VCAM-1 types, which play a prominent role in eosinophil extravasation [13].

The clinical pattern of NP is similar to that of perennial rhinitis [9], and the symptoms become more severe upon stimulation by an irritant [14]. Positive skin prick test (SPT) results have been observed in 55% of patients with NP [5], and 16%-25% of patients with NP have been observed to exhibit increased levels of airborne allergen-specific IgE compared with 12.5% in controls [15]. In addition, patients with allergic rhinitis are roughly 6 times more likely to develop NP than the general population [16]. Scavuzzo et al [10] studied atopic patients with polyps and found significant differences with nonatopic patients (higher concentrations of total IgE

and IL-8). These findings suggest that inflammation is still a major factor in the etiology of NP and reveal different levels of inflammatory mediators in atopic and nonatopic patients.

Nonatopic and atopic patients' polyps have different immunological patterns. Type 1 helper T cells (T<sub>H</sub>1) are predominant in nasal polyp tissue. Polyps from atopic patients had more T<sub>H</sub>2 cells and eosinophils than those from nonatopic patients. Eosinophil recruitment in NP is probably associated with T<sub>H</sub>2 cell infiltration [17]. Recent studies have sought to confirm whether eosinophil-mediated inflammatory processes are due to the action of specific allergens such as fungi [18,19], food [1], or bacterial superantigens [20-22].

The aim of this study was to identify the association between allergic factors in NP by examining hypersensitivity reactions to common allergens and environmental exposure potentially contributing to the phenomenon.

## Material and Methods

We conducted a cut-off comparative study involving 190 patients with NP and 190 healthy individuals (controls) with no chronic rhinosinusitis or NP, as ruled out by nasal endoscopy. Diagnosis of NP was based on the EP3OS classification [23], with bilateral polyps revealed by nasal endoscopy. The patients, aged 18 years or older, were seen at the Outpatients Service of the Reina Sofía University Hospital (Córdoba, Spain) between October 2004 and December 2006. Any patients diagnosed with cystic fibrosis, antrochoanal polyps, or other nasal tumors were excluded.

The diagnostic methods used were as follows:

- A predesigned clinical form consisting of 4 sections: family history, personal history, present clinical symptoms, and environmental exposure
- Skin prick testing to 18 inhaled allergens

Prick tests were performed using standardized Allergy Pricker steel lancets (Dome Hollister Stier, Spokane, Washington, USA). Responses were deemed positive in accordance with the recommendations of the Subcommittee on Allergen Standardization and Skin Tests of the European Academy of Allergy and Clinical Immunology (EAACI). Thus, a reaction was taken to be positive if the resulting papule was as large as or larger than that produced by the positive control (histamine). Negative controls consisted of glycerin-containing saline. The allergenic extracts used were those of the commercial battery CBF LETI (Alergia, SA, Barcelona, Spain).

The study was approved by the local ethics committee and each participant signed an informed consent form.

## Results

### *Epidemiological Variables*

The patient group comprised 121 males (63.7%) and 69 females (36.3%). The mean (SD) age of the group was 48.2 (15.1) years (men 49.8 years and women 45.5 years; range, 19-88 years). The interquartile range was 37 to 61. A family history of allergy was

recorded in 62.1% (118/190) of patients, and 30.5% (58 cases) had more than one first-degree relative with atopy. Fifty-one controls (26.8%) had a family history of allergy.

Bronchial asthma was the most prevalent pathological entity among the patients; in fact, 81 cases (42.6%) had previously been diagnosed as asthmatic. In addition, 13.1% of the patients with no previous diagnosis of the disease exhibited occasional dyspnea, recurrent cough, and/or wheeze during examination. These individuals underwent respiratory function tests with bronchodilators. The results were positive in 12 cases; therefore, the actual incidence of bronchial asthma among the patients was 93 cases (48.9%). By contrast, only 2.1% of the controls (4 individuals) were asthmatic. A chi-square test revealed the presence of statistically significant differences at  $P < .001$  and provided an odds ratio of 58.7 (95% confidence interval [CI], 20.9-164.5).

A particularly prevalent clinical entity among the patients was sensitivity to acetylsalicylic acid, which affected 47 patients (24.7%) and only 1 control. Similarly, 43 patients (22.6%) had Widal syndrome.

### Clinical Variables

The mean duration of the symptoms in the patient group was 12.7 (7.5) years (range, 2-39). The most frequent symptoms are summarized in Table 1. The patients also exhibited other skin diseases including urticaria (46 cases vs 12 controls, 24.2% vs 6.3%) and eczema (19 cases vs 9 controls, 10% vs 4.7%).

### Environmental Exposure

The patient group encompassed a wide range of occupations, the most common being farmer (17.9%), homemaker (16.8%),

Table 1. Symptoms Most Frequently Observed in the Patient Group

Symptoms	Patients	%
Anosmia-hyposmia	153	80.5%
Rhinorrhea	147	77.4%
• Hydrorrhea	98	66.7%
• Mucosal rhinorrhea	32	21.8%
• Purulent rhinorrhea	17	11.5%
Nasal blocking	137	72.1%
Sneezing	116	61.1%
Nasoconjunctival itch	114	60.0%
Headache	98	51.6%
Cachosmia	57	30.0%

office worker (12.6%), building worker (7.4%), and mechanic (5.3%).

The distribution of patients according to dwelling type and location was very homogeneous. Thus, 101 individuals (53.2%) lived in a city, most (82.6%) on the second, first, or ground floor. Most of the dwellings (74.2%) were normal or dry in terms of humidity. The figures for the control group were very similar, with no statistically significant differences in either group.

We studied contact with animals in both groups. The patients were in regular contact with various kinds of animals including dogs (57 cases, 30%), cats (29 cases, 15.3%), birds (53 cases, 27.9%), and miscellaneous other species (15 cases, 7.9%); more than 20% of patients were in contact with more than 1 animal. By contrast, 73 patients (38.4%) had no regular contact with animals.

Table 2. Proportions of Patients and Controls Testing Positive in Skin Prick Tests With Airborne Allergens and Statistical Significance of the Results.

Allergen	Patients	Controls	P
<i>Dermatophagoides pteronyssinus</i>	52 (27.7%)	28 (14.8%)	.002
<i>Dermatophagoides farinae</i>	41 (21.3%)	221 (11.2%)	.008
<i>Olea europaea</i>	40 (21.1%)	17 (9.0%)	.001
<i>Platanus acerifolia</i>	26 (13.8%)	11 (5.9%)	.014
<i>Cupressus arizonica</i>	15 (7.9%)	4 (2.1%)	.01
Grasses (group)	35 (18.5%)	23 (12.2%)	.089
<i>Artemisia vulgaris</i>	16 (8.5%)	6 (3.2%)	.029
<i>Parietaria judaica</i>	6 (3.2%)	2 (1.1%)	.174
<i>Plantago lanceolata</i>	14 (7.4%)	7 (3.7%)	.122
<i>Salsola kali</i>	18 (9.5%)	1 (0.5%)	<.001
Dog dander	18 (9.5%)	6 (3.2%)	.012
Cat dander	17 (9%)	8 (4.2%)	.066
Cockroach (group)	34 (18%)	11 (5.8%)	<.001
<i>Alternaria alternata</i>	13 (6.8%)	6 (3.2%)	.66
<i>Aspergillus fumigatus</i>	13 (6.8%)	0 (0.0%)	.001
<i>Cladosporium herbarum</i>	8 (4.2%)	1 (0.5%)	.22
<i>Penicillium notatum</i>	12 (6.3%)	3 (1.6%)	.1
<i>Candida albicans</i>	16 (8.4%)	3 (1.6%)	.07

We also examined the relationship between the onset of symptoms or their worsening in the patients who had contact with various environmental factors. No such relationship was detected in 35 patients (18.4%). The factors most frequently inducing symptoms in the patients were weather changes (64.7%), extreme temperatures (48.4%), industrial pollutants or irritants (39.5%), and ambient moisture (36.8%). We observed systematic worsening in 18.4% of patients in winter, 17.9% in spring, 5.3% in autumn, and 3.7% in summer. Symptoms appeared or worsened in different seasons in 39 patients (20.5%)—this was variable in 31 patients (16.3%). This worsening was chronic, with no clear-cut seasonality in 41 (22.1%). The most common place of onset or worsening of symptoms in the patients was anywhere (56.3%), followed by their homes (25.3%), the countryside (16.8%), and their workplace (4.7%).

### Skin Prick Testing

A total of 120 (63.2%) patients with NP had positive results and 70 (36.8%) had negative results: 29 (24.2%) were positive for a single allergen, 28 (23.3%) for 2 allergens, and 63 (52.5%) for more than 2. In the control group, skin prick test results were positive in 59 individuals (31.1%). The differences with the patient group in this respect were statistically significant ( $P < .001$ ). Eighteen (25.4%) of the previous 59 individuals tested positive for a single allergen, 15 (25.4%) for 2, and 26 (44.1%) for more than 2.

The allergens most frequently eliciting a reaction from the patients in the skin prick tests were as follows: *Dermatophagoides pteronyssinus* (27.7%), *Dermatophagoides farinae* (21.3%), *Olea europaea* (21.1%), and grasses (18.5%). The corresponding allergens for the controls were *D pteronyssinus* (14.8%), grasses (12.2%), *D farinae* (11.2%), and *O europaea* (9%). Differences were statistically significant for all allergens except grasses (*Parietaria judaica*, *Plantago lanceolata*, *Alternaria alternata*, *Cladosporium herbarum*), fungi (*Penicillium notatum*, *Candida albicans*), and cat dander (Table 2).

## Discussion

The origin of NP is highly controversial and has been the subject of many theories and assumptions [24], although in recent years, an allergic origin has been favored. The incidence of allergy in patients with NP has been found to range from 10% to 96.5% depending on the study [25,26]. Although patients frequently give positive skin prick test results, the potential role of IgE-mediated hypersensitivity in the formation of polyps is based on contradictory results.

In 1971, Caplin et al [13] found that only 0.5% of 3000 allergic patients had NP. Mygind et al [27] found no increased prevalence of atopy in patients with polyposis relative to the general population. Drake-Lee et al [28,29] found no increased incidence of allergy among the study patients or any significant differences in histamine levels in polyps from patients with and without allergic rhinitis.

However, Asero and Bottazi [2], Bernstein et al [30,31],

and Pang et al [1] continue to deem allergy a predisposing factor for NP: the first authors found that 40% of patients (vs only 1% of the controls) tested positive for *C albicans*, and the second found that 81% of patients (versus 11% of the controls) did so for food allergens. In 2001, Bachert et al [32] suggested a potential local allergy in the nasal mucosa caused by increased total and specific IgE in polyps, although there was no systemic manifestation of allergy.

In terms of the immune system, NP has been ascribed to inflammatory phenomena potentially caused by allergy. In the present work, we studied allergy reports in both patients and controls and found them to exhibit significant differences in this respect. Thus, 62.1% of patients had some first-degree relative (parent, sibling, offspring) with known atopy (most frequently to dust mites, grasses, or olive pollen) in contrast to only 26.8% of controls. Few studies on family histories of allergy in patients with polyposis have been reported to date. Pumhirum et al [16] found 48% of patients with a family history of atopy—a value similar to ours—compared with 33% of controls.

In a study on the prevalence of polyposis in France, Klossek et al [33] found allergy to be significantly more frequent in the patient group than in the control group; many patients were aware of their allergy (27.1% vs 11.9%) or sensitivity to acetylsalicylic acid (20.3% vs 4.3%). These figures are similar to ours.

Regarding environmental factors, we found no significant differences in dwelling type between the groups or in occupation between patients. This seems to rule out a potential relationship between occupational exposure and NP. Both groups were similarly exposed to contact with animals. Clinical seasonality exhibited a very homogeneous distribution; thus, 20% of patients exhibited symptoms in different seasons and 38% had perennial symptoms or crises, that did not follow a clear-cut seasonal pattern. The environmental factors most closely related to the onset or worsening of symptoms were weather and temperature changes, and the presence of industrial pollutants and irritants.

As regards the place of onset or worsening of symptoms, most patients failed to associate theirs with any in particular. The potential relationship between environmental factors and NP has scarcely been investigated. In one study [34], patients using wood-burning stoves were found to be especially prone to develop polyps, which were ascribed to the presence of environmental pollutants. According to Settupane et al [35], however, no differences in polyp incidence arising from climatic, regional, or social and economic differences appear to exist.

NP has a considerable impact on quality of life, and atopy worsens this impact. Alobid et al [36] evaluated the association between quality of life and atopy, sinus opacification, and nasal patency in severe NP. Atopic patients had worse scores in terms of physical pain, vitality, and mental health than nonatopic patients.

The results of our skin prick tests were significantly different between the 2 groups—63.2% of patients tested positive for at least 1 allergen—and the patients were roughly twice as likely to be allergic as the controls.

Some authors [33,35] show that up to 55% of patients with

NP have positive results for various allergens in skin prick testing. Nevertheless, these tests give a high number of positive results among the general population as well. The proportion of patients with NP and positive skin test results [28,36-40] ranges from 24% to 75%.

The results of our skin tests revealed significant differences for most of the allergens studied. The allergens most frequently resulting in sensitization in both groups were dust mites (*D pteronyssinus* and *D farinae*), and the differences were statistically significant.

The second allergen in terms of sensitizing capacity in this study was *O europaea*. Other allergens causing extensive sensitization were grasses (*Cynodon dactylon*, *Festuca elatior*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*), animal dander and allergenic proteins such as those in the cockroach group (*Blattella germanica*, *Blatta orientalis*, and *Periplaneta americana*), and cat and dog dander. Interestingly, the highest incidence of sensitization in the patient group coincided with the most prevalent allergens—whether seasonal or perennial—in the study area.

Some studies [41,42] have revealed extensive sensitization, especially to dust mites (about 80% in patients with NP, which is a much higher percentage than that observed in our series). All patients with polyposis in a study by Pumphurum et al [16] exhibited atopic symptoms and 48%—a proportion similar to ours—had a family history of atopy; by contrast, 36.6% of their controls had allergic symptoms and 33% a family history of atopy. Positive skin test results, especially for *D pteronyssinus*, *D farinae*, and the cockroach group, were observed in 60% of patients. According to the authors, these results allowed two-thirds of the patients to be diagnosed as allergic—an outcome similar to ours.

The fungal allergens most commonly eliciting a reaction in the prick tests were *Aspergillus fumigatus* and *P notatum*. On the other hand, *A alternata* exhibited statistically nonsignificant differences, as did *C herbarum*, *P notatum*, and *C albicans*. Our results are lower than those of other authors [2,17,19,43]. The allergenic role of fungi remains unclear, as no standard extracts for reliable skin and in vitro testing are available. Moreover, this testing is rarely performed on a routine basis, with the result that little epidemiological evidence can be derived from it.

Asero et al [2] showed that 55% of patients with polyposis exhibited skin reactivity to at least 1 allergen. Nearly half reacted to fungi (particularly *C albicans*). However, the authors questioned the allergenicity of this fungus and hypothesized that the response of their patients might in fact have been a non-specific, non-IgE-mediated inflammatory reaction of the skin upon inoculation of the allergenic extract.

Stroud et al [43] performed a comparative study where 85% of the patients exhibited increased skin reactivity to common allergens compared with only 33% of the controls. Dust mites were the most prevalent allergen in both groups. The individual fungus eliciting the greatest reactivity was *Fusarium solani*, followed by *Alternaria* and *Pullularia* species. These values are higher than those we observed.

Bronchial asthma was the most prevalent condition in the clinical histories of our patients, and the differences with the control group were significant. The clinical profile

for the patients who were allergic to *O europaea* [44,45] was previously found to include an increased incidence of bronchial asthma and perennial symptoms, even though this is a seasonal allergen. Some studies [46,47] have revealed an increased incidence of asthma in patients with allergy to olive pollen; however, no studies to date have focussed on the presence of chronic rhinosinusitis associated with bronchial asthma. The authors of these studies hypothesize that the increased frequency of bronchial asthma in patients allergic to *O europaea* is due to the fact that the most hyperreactive individuals are those exhibiting atopic symptoms to the most frequent allergens in their environment [48,49].

Therefore, it is not the characteristics of the antigen that facilitate the development of asthma and NP, but the environmental antigens that act on hyperreactive individuals. In summary, patients with NP are more reactive to allergens than the general population, which suggests that IgE-mediated hypersensitivity plays a role in the development of the disease.

Our patients with NP were sensitized to the most common allergens in our environment. Their personal and family histories and the results of in vivo tests revealed a close relationship with other allergic factors and a clinical picture including perennial rhinitis. However, none of the environmental exposure or seasonal factors examined appears to have contributed to the development of NP in these patients. In summary, NP is a condition involving self-perpetuating chronic inflammatory phenomena. Its exact origin is unknown, although several factors are involved in its etiology. Allergy is a contributing factor, but its exact role cannot be identified at the moment.

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