ORIGINAL ARTICLE

Clinical Management and Use of Health Care Resources in the Treatment of Nasal Polyposis in Spanish Allergy Centers: The POLAR Study

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Abstract

Background: Nasal polyposis (NP) is a chronic inflammatory disease that constitutes a major health problem with significant comorbidities and a considerable associated socioeconomic burden.
Objective: To describe the clinical features and management of patients with NP attending Spanish allergy centers, the use of health care resources, and the degree of compliance with the diagnostic and therapeutic recommendations of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS).
Methods: We performed a multicenter, observational, and cross-sectional epidemiologic study of 671 patients consulting for NP in 67 Spanish allergy departments. We used sociodemographic and clinical questionnaires to evaluate clinical characteristics, use of health care resources, diagnostic methods, and treatment administered.
Results: NP was closely associated with asthma (66%), allergic rhinitis (45.9%), and hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) (26%). Atopy was present in the 50% of cases, with *Dermatophagoides pteronyssinus* as the most frequent sensitizing allergen. Eleven percent of NP patients visited the emergency department during the previous year, and more than 58% used primary care,

allergy, or otorhinolaryngology services. The most frequently used diagnostic tests were skin prick tests (93.6%) and anterior rhinoscopy (79.4%). Intranasal corticosteroids were the drug class most frequently prescribed by allergists (74.6%). Specific immunotherapy was prescribed in 21% of patients.
Conclusions: NP is a chronic inflammatory disease that generates considerable use of health care resources. The close association with atopy, asthma, and NSAID hypersensitivity highlights the usefulness of an allergy workup in all patients with NP. Analysis of the clinical management of NP by allergists in Spain revealed a high degree of compliance with EPOS diagnostic and therapeutic recommendations.
Key words: Allergological evaluation. Atopy. Health care resources. Nasal polyps. Diagnosis. Treatment.

Resumen

Introducción: La poliposis nasal es una enfermedad inflamatoria crónica asociada frecuentemente a otras enfermedades. Constituye un importante problema sanitario con un gasto económico considerable.
Objetivo: Describir las características y manejo clínico de los pólipos nasales (NP) de pacientes asistidos en los centros alergológicos españoles, incluido el consumo de recursos sanitarios, y el grado de cumplimiento de los esquemas diagnósticos y terapéuticos del documento europeo de consenso sobre rinosinusitis y pólipos nasales (EPOS).
Métodos: Estudio epidemiológico multicéntrico, observacional y transversal. Se estudiaron 671 pacientes con NP atendidos en 67 servicios de Alergología de España. Las características clínicas, el consumo de recursos sanitarios, los métodos diagnósticos y el tratamiento se evaluaron mediante cuestionarios sociodemográficos y clínicos.
Resultados: Se detectó una alta asociación entre NP y asma (66%), rinitis alérgica (45,9%) e hipersensibilidad a antiinflamatorios no esteroideos (AINES) (26%). Se detectó atopia en el 50% de los casos, siendo el *D. pteronyssinus* el alérgeno más frecuente. El 11% requirió asistencia en urgencias el año anterior, y más del 58% asistencia en atención primaria, alergología u otorrinolaringología. Las pruebas diagnósticas más utilizadas fueron las pruebas cutáneas (93,6%) y rinoscopia anterior (79,4%). Los corticoides intranasales (74,6%) representaron el principal tratamiento farmacológico recomendado. La inmunoterapia específica se prescribió en el 21% de los pacientes.
Conclusiones: Los NP es una enfermedad inflamatoria crónica con un elevado consumo de recursos sanitarios. La alta asociación con atopia, asma e hipersensibilidad a AINES resalta la utilidad de la evaluación alergólogica en estos pacientes. El manejo clínico de los NP por alergólogos españoles mostró un alto grado de cumplimiento con los esquemas diagnósticos y terapéuticos EPOS.
Palabras clave: Evaluación alergológica. Atopia. Recursos sanitarios. Pólipos nasales. Diagnóstico. Tratamiento.

Introduction

Nasal polyposis (NP) is a major health problem with significant comorbidities and a considerable socioeconomic burden. It is a chronic inflammatory disease with an estimated prevalence of 1.0%-4.5% in adults and 0.1% in children [1,2]. It is generally accepted that patients with NP constitute a subgroup within patients with chronic rhinosinusitis (CRS) [1,3,4], although the question of why only some CRS patients develop NP remains unanswered.

The frequent association with other diseases such as rhinitis, asthma, bronchiectasis, cystic fibrosis, hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), and atopy [5-6] emphasizes the importance of a multidisciplinary approach based on collaboration between primary care physicians (general or family medicine, pediatricians) and specialists (otorhinolaryngologists, allergologists, and pulmonologists) to ensure adequate diagnosis and management of the disease [7].

In 2005, the Spanish Society of Allergy and Clinical Immunology performed an epidemiologic study involving nearly 5000 patients seen at specialized Spanish allergy clinics [8,9]. Data were collected on clinical and epidemiological characteristics, diagnostic methods, and treatments administered by allergists. However, NP and CRS were not specifically assessed, and patients were not asked about personal or family history or about current NP and CRS. Therefore, data on NP and CRS were scarce and did not show the clinical reality of the diseases.

In the latest update of the European Position Paper on Rhinosinusitis and Nasal Polyps group (EP3OS 2007) [3] and EPOS 2012 [4], CRS with or without and NP is defined as inflammation of the nose and paranasal sinuses, and clear clinical, endoscopic, and radiologic diagnostic criteria are established.

Several epidemiological studies on CRS with and without NP have been conducted [2,10-15], but few were designed based on EP3OS criteria [14,15].

NP is nowadays considered a subtype of CRS that should be studied independently owing to its specific characteristics. In 2011, the Spanish Society of Allergy and Clinical Immunology and the Spanish Society of Otorhinolaryngology used a multidisciplinary approach to develop the POLINA Project [7], one of the few evidence-based consensus documents on NP, which specifies strict diagnostic criteria and therapy guidelines, including immunotherapy for allergic patients with NP.

The aim of the current study was to describe the clinical features and the clinical management of patients with NP attending Spanish allergy centers, including the use of health care resources in the last 12 months and the degree of compliance with EP3OS diagnostic criteria and therapy guidelines.

Methods

"Clinical and epidemiological characteristics of nasal POLyposis in AlleRgology" (POLAR) is a multicenter, observational, cross-sectional study that was conducted in 67 allergy departments in Spain between June 2008 and September 2009. All Spanish geographical regions were represented. The study protocol fulfilled the principles of the Declaration of Helsinki and was approved by the independent Ethics Committee of Carlos Haya Hospital in Málaga, Spain. The study analyzed clinical features and use of health care resources during the previous 12 months, as well as the diagnostic methods and treatments used in patients with NP attending allergy departments in Spain.

The clinical characteristics and the impact of NP on patients' quality of life were analyzed elsewhere [16].

Patients

Each investigator included 10 consecutive adult patients with NP diagnosed by clinical symptoms and computed tomography (CT) scan or nasal endoscopy (performed by allergists or otorhinolaryngologists) following EPOS clinical diagnostic criteria [4].

Patients with polyps not caused by inflammation (ie, tumors, cystic fibrosis–associated polyps, and other conditions) were excluded. All patients signed an informed consent document.

Clinical Questionnaire

Clinical data were obtained during the clinical interview at the study visit and from the patient's medical records. A detailed sociodemographic and clinical questionnaire was applied to obtain information about clinical features (severity and frequency of symptoms [data not shown], comorbidities, and use of health care resources) and clinical management (diagnostic methods and recommended treatments used in the 12 months before the study and after the allergy workup).

Allergic rhinitis was classified as persistent or intermittent, mild, and moderate-severe according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [17], and asthma was classified as intermittent, persistent mild, persistent moderate, and persistent severe following the Global Initiative for Asthma (GINA) guidelines (www.ginasthma.com). Atopy was defined by the existence of al least 1 positive skin prick test (SPT) result to locally adapted batteries of aeroallergens that had to include at least house dust mites, molds, pollens, epithelia, and cockroach. Food allergy was diagnosed by clinical history plus a positive SPT result or serum specific IgE to the food. NSAID hypersensitivity was defined following EPOS criteria [4].

Statistical Analysis

Qualitative variables were expressed using frequencies; quantitative variables were expressed using measures of central tendency and dispersion. Results were compared using the chi-square test for qualitative variables and the Mann-Whitney test for quantitative variables. A sample size of 600 patients with NP was considered necessary to achieve a 4% precision with a 95% confidence interval, taking into account a 5% loss of evaluable patients. The statistical analysis was performed using SAS version 9.2. A P value <.05 was considered significant.

Results

Clinical Features of Nasal Polyps Patients Attending Spanish Allergy Centers: Demographic and Clinical Characteristics

A total of 671 patients were recruited by 67 allergy services. Of these, 611 (91%) were evaluable, and 60 (9%) were excluded for not fulfilling the inclusion criteria. Mean age was 46 years, 49.8% were male, 36.8% had undergone polypectomy (mean of 1.76 surgical interventions per patient), and 11% had a family history of NP. A detailed overview of the patients' demographic and clinical characteristics is shown in Table 1.

Table 1. Demographic and Clinical Characteristics of Patients (N=611)

Age, mean (SD)	46.09 (13.48)
Sex, male, No. (%)	303 (49.8)
Onset age, mean (SD)	30.07 (8.51)
Polypectomy, No. (%)	225 (36.8)
Number of polypectomies, mean (SD)	1.76 (2.22)
Family history of allergic diseases, yes, No. (%)	227 (45.3)
Asthma	173 (28.3)
Rhinitis	106 (17.3)
Drug allergy	31 (5.1)
Family history of nasal polyposis, No. (%)	67 (11.0)

Comorbidities

The most frequent comorbidities were asthma (66% [397/601]), allergic rhinitis (45.9% [276/601], and NSAID hypersensitivity (26% [159/611]). The evaluation of persistence and severity of allergic rhinitis and asthma associated with NP showed that 78% of patients experienced persistent symptoms. In addition, most complained of moderate nasal symptoms (49%) and bronchial asthma symptoms (55%). Five percent of patients with persistent allergic rhinitis and 9% of patients with persistent asthma reported experiencing severe symptoms.

Atopy was present in 50% of patients (298/596). The most frequent sensitizing aeroallergens were *Dermatophagoides pteronyssinus* (61.4%) and *Dermatophagoides farinae* (49.7%), followed by grass pollen (45.3%).

Food allergy was detected in 23 patients with NP (3.8%), most of whom were sensitized to fruits (12/23, 40%); the frequency of other food sensitization was ≤4% (data not shown).

NSAID hypersensitivity (Table 2) was diagnosed in 159 patients (26%). Most cases were diagnosed through an obvious clinical history (71.7%) or using the clinical history combined with oral challenge (25.2%).

Table 2. NSAID Hypersensitivity Subtypes and Diagnostic Procedures in Patients With Nasal Polyposis

NSAID Hypersensitivity (N=159)	No. (%)
Diagnostic methods	
Clinical history	114 (71.7%)
Clinical history and oral challenge	40 (25.2%)
Clinical history and L-ASA nasal challenge	3 (1.9%)
Clinical history and L-ASA bronchial challenge	1 (0.6%)
Clinical history, L-ASA bronchial and oral challenge	1 (0.6%)

Abbreviations: L-ASA, lysine acetylsalicylate; NSAID, nonsteroidal anti-inflammatory drug.

Use of Health Care Resources

The analysis of the use of health care resources in the previous year revealed that 11% of NP patients had attended the emergency department (mean [SD] number of visits [MNV], 1.2 [1.2]), more than 73% had attended primary care (MNV, 3.5 [3.4]) and allergy departments (MNV, 1.9 [1.2]), and 58.9% were evaluated by an otorhinolaryngologist (MNV, 1.9 [1.4]) (Table 3).

Clinical Management of Patients with NP Attending Spanish Allergy Centers

Diagnostic Procedures

After the clinical history, SPT was the main diagnostic procedure performed by Spanish allergists in patients with NP (Table 4). When diagnostic methods were analyzed separately, we observed that SPT (93.6%), serum total IgE (70.5%), and serum specific IgE (58.3%) were the most frequent allergy examinations. The most frequent rhinology examinations were anterior rhinoscopy (79.4%) and nasal endoscopy (7%), and the most common imaging tests were CT (40.1%) and x-ray of the nose and sinuses (19.3%). Spirometry was performed in 55.6% of patients, controlled oral drug provocation tests in 12.6% of patients, and nasal allergen provocation tests (NAPT) in 3.1%. More detailed data are shown in Table 4. A total of 59.8% of NP patients were diagnosed by otorhinolaryngologists using nasal endoscopy and/or CT scan and sent for evaluation to allergy services.

Table 3. Use of Health Resources by Patients With NP in the Last 12 Months

Health Services	Total
Primary care	
Yes, No. (%)	447 (73.2)
Visits, Mean (SD)	3.5 (3.4)
Median	3
Allergologist	
Yes, No. (%)	487 (79.7)
Visits, mean (SD)	1.9 (1.2)
Median	2.0
Otorhinolaryngologist	
Yes, No. (%)	360 (58.9)
Visits, mean (SD)	1.9 (1.4)
Median	2.0
Pulmonologist	
Yes, No. (%)	73 (11.9)
Visits, mean (SD)	1.3 (1.7)
Median	1.0
Emergency	
Yes, No. (%)	67 (11.0)
Visits, mean (SD)	1.2 (1.2)
Median	1.0
Other	
Yes, No. (%)	23 (3.8)
Visits, mean (SD)	2.0 (2.7)
Median	1.0

Abbreviation: NP, nasal polyposis.

Table 4. Diagnostic Methods Performed by Allergists in Nasal Polyposis

Diagnostic Methods	No. (%)
Immuno-allergological tests	
Skin prick test	572 (93.6)
Serum total IgE	431 (70.5)
Blood count and biochemistry	359 (58.8)
Serum specific aeroallergen IgE	356 (58.3)
Drug provocation test	77 (12.6)
α-1-Antitrypsin	27 (4.4)
Nasal allergen provocation test	19 (3.1)
IgA secretory	10 (1.6)
Serum SAE specific IgE	7 (1.1)
Nasal examination	
Anterior rhinoscopy	485 (79.4)
Nasal cytology	76 (12.4)
Nasal endoscopy	43 (7.0)
Acoustic rhinometry	31 (5.1)
Nasal nitric oxide	19 (3.1)
Anterior active rhinomanometry	14 (2.3)
Nasal lavage	11 (1.8)
Nasal peak inspiratory flow	5 (0.8)
Olfactometry	1 (0.2)
Spirometry	340 (55.6)
Imaging	
Computed tomography	245 (40.1)
Plain x-ray	118 (19.3)

Abbreviation: SAE, *Staphylococcus aureus* enterotoxin.

Medical Management

Before consultation, 86% of patients with NP had received medical treatment. The most frequently used pharmacologic agents were topical corticosteroids (60.8%), oral antihistamines (39.1%), and antileukotrienes (15.9%) (Table 5).

Comparison of prescription of medical treatment before and after the study visit showed that allergists significantly extended the recommendation of medical treatment to up to 95% of patients (P=.037). A detailed analysis of the therapy recommended by allergists revealed a significant increase in the prescription of intranasal corticosteroids (74.6%, P<.001), oral antihistamines (49.4%, P<.001), and antileukotrienes (24.2%, P<.001), as well as a significant reduction in the prescription of intranasal decongestants (2.6% to 0.3%, P=.005) and a nonsignificant reduction in the prescription of systemic

Table 5. Treatment for Nasal Polyposis Prescribed by Nonallergists and Allergists[a]

Treatment	Non-allergist No. (%)	Allergist No. (%)	*P* Value	OR (95%CI)
Decongestants	32 (5.2)	24 (3.9)	.275	0.740 (0.431-1.271)
Oral	16 (2.6)	22 (3.6)	.325	0.720 (0.374-1.385)
Intranasal	16 (2.6)	2 (0.3)	.005	0.122 (0.028-0.534)
Antibiotics	15 (2.5)	13 (2.1)	.702	0.864 (0.408-1.831)
Corticosteroids	391 (64.0)	483 (79.1)	<.001	2.123 (1.645-2.741)
Systemic	15 (2.5)	9 (1.5)	.221	0.594 (0.258-1.368)
Intranasal	372 (60.8)	456 (74.6)	<.001	1.890 (1.481-2.413)
Both	2 (0.3)	2 (0.3)	1.000	1.000 (0.140-7.122)
Antihistamines	239 (39.1)	302 (49.4)	<.001	1.521 (1.212-1.909)
Oral	239 (39.1)	302 (49.4)	<.001	1.521 (1.212-1.909)
Intranasal	6 (0.9)	5 (0.8)	.762	0.832 (0.253-2.741)
Antileukotrienes	97 (15.9)	148 (24.2)	<.001	1.694 (1.274-2.253)

[a]The data shown are those with a frequency of at least 5%.

corticosteroids (2.5% to 1.5%, *P*=.221). The most frequently prescribed intranasal corticosteroids were fluticasone (32%) and mometasone furoate (30%). The second-generation oral antihistamines desloratadine (16%), rupatadine (9%), and levocetirizine (8%) were the most frequently prescribed oral antihistamines.

Allergists recommended specific subcutaneous immunotherapy to 20.9% of patients with respiratory allergy (67/320), and the most frequent allergen composition was 100% *D pteronyssinus* (19 patients, 39%). Specific sublingual immunotherapy was not prescribed.

Discussion

The present study was conducted in 67 allergy departments throughout Spain and involved 611 patients. To our knowledge, this is the largest epidemiologic study on patients with NP.

Previous studies have shown the frequency of atopy to range from 10% to 64% in NP patients [1]. We found atopy to be present in 50% of patients, and, according to previous data, *D pteronyssinus, D farinae*, and grasses were the most frequent sensitizing allergens [18]. Several studies have demonstrated an association between atopy and NP [2,18-20]; however, the true clinical relevance of sensitization by aeroallergens in NP should be further evaluated. The presence of SPT positivity and allergic respiratory disease are different concepts; therefore, the clinical relevance of either a positive or negative SPT result should always be established in the context of the clinical history, which should be complemented by NAPT in cases with no concordance between the clinical history and SPT results [21,22].

Respiratory allergy (rhinitis and/or asthma) and NSAID hypersensitivity impair patients' quality of life and have been associated with severe forms of NP [3-5,7,13,14,23]. Since a high percentage of patients in the present study had asthma (66%), allergic rhinitis (45.9%), and/or NSAID hypersensitivity (26%), correct diagnosis and treatment of these comorbidities would improve the quality of life of patients with NP.

The recent finding of a local allergic response in patients with NP and specific IgE (sIgE) in the mucosa but not in peripheral blood has been proposed as a possible etiological factor in the development of NP [24-26]. Moreover, Sabirov et al [27] detected a correlation between the level of *Alternaria* sIgE and eosinophil cationic protein in nasal polyps, suggesting that localized IgE-dependent eosinophilic degranulation could play a role in the pathogenesis of NP. More recently Gevaert et al [26] provided the first evidence of local receptor revision, class switching to IgE, and B-cell differentiation to IgE-secreting plasma cells in NP. These data demonstrate that an advanced allergy study of the target organ with nasal detection of sIgE antibodies and/or NAPT is essential for the diagnosis of a local IgE-mediated allergic response in patients with NP and for the identification of forms characterized by severe eosinophilic inflammation.

We show that NP is a chronic inflammatory disease with frequent exacerbations and marked use of health care resources. Thus, in the 12 months before the study, more than 58% of NP patients required 2 or more visits to primary care, allergists, or otorhinolaryngologists, and 11% of patients required 1 visit to the emergency department.

As the main objective of this study was to describe the clinical features and management of NP patients attending Spanish allergy centers, the patients included were those who had been sent to allergy centers. Consequently, and despite the lack of selection bias, the study results do not reflect the characteristics of patients with NP in the general population.

Allergological management of NP in Spain shows that clinical history, SPT, anterior rhinoscopy, and CT were the most frequent diagnostic methods used. However, nasal endoscopy, which covers the entire nasal passage [3], was only carried out by an allergist in 7% of patients. Since anterior rhinoscopy covers the anterior third of the nasal passages, only large nasal polyps can be visualized. However, the technique remains the first step in the evaluation of patients with NP by primary care physicians and specialists other than otorhinolaryngologists. These results indicate that increased use of nasal endoscopy by Spanish allergists could improve the diagnosis of NP and help to assess the response to medical and surgical treatments.

According to the treatment schedules recommended in the EPOS 2012 document [4], intranasal corticosteroids, the first-line treatment in NP and CRS, were the drug class most frequently recommended by Spanish allergists. The most prescribed intranasal corticosteroids were fluticasone and mometasone furoate. Both forms have low systemic bioavailability and high liposolubility, which facilitate tissue permanence for more than 24 hours, a major advantage in the long-term treatment of conditions such as CRS with/without NP [3,7]. Nasal douches and oral antihistamines were also frequently prescribed, with a predominance of second-generation oral antihistamines (desloratadine, rupatadine, and levocetirizine), as recommended in the ARIA consensus [17].

We also evaluated whether medical treatment for NP differed between allergists and primary care physicians and observed that allergists prescribed a significantly higher percentage of intranasal corticosteroids, oral antihistamines, and antileukotrienes. These data could reflect the fact that despite efforts to disseminate the 2012 EPOS guideline [4], the information does not reach primary care physicians and allergists to the same extent. Similar data were recently reported on adherence by nonexperts to urticaria treatment guidelines [28].

Specific subcutaneous immunotherapy was prescribed to 20.9% of patients with respiratory allergy, with *D pteronyssinus* as the most frequent sensitizing allergen and the most frequent immunotherapy allergen extract. The role of specific immunotherapy in NP is not clear. Presurgical specific immunotherapy has been reported to improve the success rate of surgery [29,30]. Nevertheless, just as antihistamines are considered adequate treatment in NP associated with allergic rhinitis [3,4,7], specific immunotherapy may also be helpful in patients with NP and allergic rhinitis and/or associated allergic asthma. Further studies are needed to evaluate the usefulness of specific immunotherapy in these cases.

Our findings demonstrate that NP is an important health problem with high socioeconomic and health costs. Multidisciplinary and coordinated treatment based on collaboration between the various health care levels is essential in prevalent chronic diseases such as NP, which frequently co-occurs with other equally prevalent and debilitating diseases.

In conclusion, we present the results of the largest epidemiologic study to date on NP in Spain and provide an overview of clinical data, comorbidities, and clinical management of NP in allergy departments. More than 90% of Spanish allergists followed the recommendations on diagnosis and treatment made in the EPOS 2012 document. The strong association between NP and rhinitis, asthma, atopy, and NSAID hypersensitivity highlights the role of the allergy workup in the diagnosis and treatment of NP and associated allergic diseases and in the evaluation of the clinical relevance of sensitization detected by SPT and local production of specific IgE antibodies in the mucosa of the nose and sinuses.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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