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Epidemiological and clinical aspects of nasal polyposis in France; the ORLI group experience*

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SUMMARY

Nasal polyposis (NP) is a common condition in patients consulting ENT practitioners in France. A multicenter prospective study was performed to evaluate symptoms, demography, environmental factors, personal and family history and associated conditions like asthma, and food or drugs sensitivity (FDS) in patients suffering from NP. In each investigation center assessments were performed at the moment of the initial consultation by the same investigator, then updated with complementary exploration results required by the protocol. The χ^2 test and the Fisher test were used for statistical analysis. In this study 224 patients were included. Males were predominant at 63%. Asthma was found in 45% of cases without relevant sex difference. However, FDS, positive in 31% of the patients, was statistically higher in females than in males (42.9% vs. 24.4%). Severe and major symptoms were more frequently found in the female population. Environment and habitat factors did not appear to be relevant. High rates of NP (52.66%) and asthma (43.58%) were found in the family history. Hereditary factors were suggested and lead us to further study the genetic factors potentially involved in this pathology.

Key words: polyposis, asthma, sensitivity, epidemiology, heredity

INTRODUCTION

Nasal polyposis (NP) can be defined as a chronic inflammatory disease of the nasal and sinus mucosa leading to diffuse formation of benign polyps protruding from sinuses into the nasal cavity. Recently, progress has been made in understanding the role of cellular and molecular factors in the physiopathology of the NP. However, the etiology of the NP is still unknown.

The recurrences and chronicity of this disease interferes with the quality of life of patients. Usual symptoms are chronic nasal congestion, smell loss, rhinorrhea, and sneezing. When present, associated conditions like asthma, food (sulfites, coloring agents) and drugs (aspirin and aspirin-like) sensitivity (FDS) seem to aggravate NP's natural history. There is a large variability of the onset and natural history of the NP and certain patients appear to tolerate the disease better than others. Few epidemiological studies on this subject are available (Braun et al., 1992; Hosen et al., 1994; Settipane, 1996; Larsen, 1996).

The rationale for this present study was to evaluate signs and symptoms of patients with NP in function of demography, environment, personal and family history, and existing associated conditions.

PATIENTS AND METHODS

Patient population and study design

This is a prospective study, conducted from 1991 to 1996 in six university ENT centers in France (Arles, Bordeaux, Montpellier, Créteil, Poitiers, Toulouse) by the ORLI group (Oto-Rhino-Laryngological Inflammation study group). In order to obtain a consensual approach, physical examination, diagnosis and complementary exploration techniques were predefined by the ORLI group and adopted by all the investigators participating in this study.

Male and female patients with bilateral nasal polyposis at nasal endoscopy were enrolled in the study. Coronal and axial CT-scan was required by the protocol. Allergy tests (prick-tests

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and/or RAST) were also performed.
Patients presenting unilateral polyposis at nasal endoscopy and no opacities in the opposite ethmoid cells on CT-scan were excluded from this study.

Assessments
A questionnaire containing over 200 items was created for data assessment.
In each investigation center, assessments were performed at the moment of the first consultation by the same investigator, then updated with complementary explorations results required by the protocol.
Demographic and environmental data, onset type, natural history, previous treatments and personal history were recorded by the investigators. Family history of NP, asthma, FDS, and nasal non-specific hyper reactivity (NHR = sneezing, nasal congestion and nasal discharge spontaneously or induced by non-specific agents) was recorded for each patient. Family history was assessed over three generations of the direct family of the patient (grandparents-parents-siblings, or parents-siblings-children).
Assessed symptoms were nasal congestion, rhinorrhea, sneezing, smell loss and facial pain. Each symptom was recorded as unilateral / bilateral and scored as absent, mild, moderate or severe. Anosmiant (A-NHR) and non-anosmiant (NA-NHR) non-specific nasal hyper reactivity, pulmonary symptoms (asthma, bronchorrhea) and clinical evidence of FDS were also assessed.
The morphology of nasal cavities, the size of the polyps and the nasal secretions were evaluated by endoscopy. A nasal polyps size-staging widely used in France (stage I - polyps in the middle meatus, stage II - polyps reaching the inferior aspect of the middle turbinate, stage III - polyps reaching the inferior turbinate or larger) was adopted for this study.
CT-scan images were recorded for each sinus cell as normal, muco-periostal thickening, partial or total opacification. When surgery was performed, macroscopic appearance of the sinus mucosa was recorded.

Statistical analysis
The questionnaire data was computer loaded using a specific clinical trial software (ClinDM) and saved in a ORACLE database. Statistical analysis was performed by a specialized company using the 6.11 SAS software.
Primary statistical analysis included demography, environment, personal and family history, NHR, asthma, allergy and FDS data. These items were analyzed in function of the polyps size-staging and of the sex distribution, then compared using the χ^2 test and the Fisher test. Sex distribution of patients enrolled in our study was compared with the last census data taken in France in 1991 and with the sex distribution of patients in one of the investigation centers (Créteil) between 1991 and 1996 for any ENT reasons.

RESULTS
Patient demographics and disposition
In this study 224 patients were included. Investigation center distribution of patients is presented in Table 1. The average age at the beginning of the study was 46, ranging from 14 to 73.

Table 1. Distribution of patients in the 6 investigation centers in France.

Investigation Center	**N**	**%**
Toulouse	59	26.34
Créteil	56	25.00
Arles	43	19.20
Poitiers	30	13.39
Bordeaux	29	12.95
Montpellier	7	3.13

There were 139 male patients (62.90%), 82 female patients (37.10%) while data was missing for 3 patients. The sex ratio (M/F) was 1.69. The percentage males in our study was significantly higher ($p<0.001$) compared with the last census data taken in France in 1991 (48.7% men and 51,3% women). When compared with the sex distribution of patients in one of the investigation centers between 1991 and 1996 for any ENT pathology (63.7% female and 36.3% male), the difference was again significant.
No correlation appeared regarding the habitat and the pollution at work (Table 2).
Thirty-four patients (15.45%) were smokers and 186 (85.55%) were non-smokers. Data were missing for 4 patients.

Table 2. Habitat, pollution at work and smoking.

Characteristics	**N**	**%**
Urban population	118	53.39
Rural population	103	46.61
missing data=3		
Pollution at work	103	46.60
No pollution at work	118	53.39
missing data=3		
Smokers	34	15.45
Non-smokers	186	85.55
missing data=4		

Personal history
NHR was found in 185 patients (83%).
One hundred patients (44.64%) had asthma. To confirm asthma in patients presenting uncertain history or with no previous test, functional respiratory tests were performed in 118 patients

and were positive in 63. Bronchial challenge was needed in 57 patients and was positive in 21.

FDS was found in 67/215 patients (31.16%). Incriminated agents for FDS were aspirin (44%), alimentary additives like sulfites, metabisulfites, coloring agents (12%), non-steroidal anti-inflammatory drugs (4%) or associations of these (40%). Clinical expressions of FDS were asthma crisis (64%), NHR and/or frontal headache (19%), Quincke edema (15.63) and various associations (1.37%).

History of respiratory allergy was found in 65/221 patients (29.41%). To confirm allergy history, prick-tests were performed in 133 patients and were positive in 52.

The family history

Family history data was available for NP in 150 patients, for asthma in 156, for FDS and NA-NHR in 131, and for A-NHR in 122 patients.

Seventy nine patients (52.66%) had at least one member in their immediate three-generation-family suffering from NP (Table 3).

Family history of asthma (Table 4), A-NHR, NA-NHR, and FDS was found respectively in 68 (43.58%), 29 (23.77%), 38 (29%) and 16 (12.21%) patients.

The score for infectious chronic bronchitis (CB) was 5/118 (4.24%).

Table 3. Family history of NP.

Family members with NP	N	%
0	71	47.33
1	62	41.33
2	10	6.67
3	5	3.33
4	1	0.67
7	1	0.67

Clinical onset and natural history of the NP and asthma

In 122/223 cases (55%) the clinical onset of the NP was marked by nasal congestion. For the other patients, the first symptoms to occur were NHR (27/223 i.e. 12.16%), smell loss (5/223 i.e. 2.25%) or associations like nasal congestion and smell loss in 22/223 (9.86%).

The onset was qualified as insidious by 153/221 patients (69.23%) and as sudden by 50/221 patients (22.62%).

NP's natural history was estimated as follows: worsening in 125/219 cases (57.08%), constant in 60/219 cases (27.40%) and recurrent in 34/219 cases (15.53%).

Asthma onset was sudden (severe crisis) for 45/100 patients (45%) and the natural history was constant for 47/96 patients (49%).

Chronology of the onset NP and asthma was found as follows: Asthma symptoms occurred first in 43/100 patients (43%). The onset was concomitant in 30/100 (30%) and asthma started after NP in 21/100 patients (21%). Six patients couldn't remember which symptoms occurred first.

Table 4. Family history of asthma.

Family members with asthma	N	%
0	88	56.41
1	48	30.77
2	14	8.97
3	1	0.64
4	5	3.21

The nasal symptoms were bilateral for 205/222 patients (92.34%) and consisted, in order of frequency, in nasal congestion, smell loss, rhinorrhea, and sneezing (Table 5).

Table 5. Rhinologic symptoms of patients with NP.

Symptoms	N	%
Nasal congestion		
Important	93	41.89
Moderate	82	36.94
Minor	39	17.57
Absent	7	3.60
Missing data = 2		
Smell		
Permanent Anosmia	118	52.91
Intermittent Anosmia > 6 days	42	18.83
Hypo-anosmia < 6 days	37	16.59
Normal	26	11.66
Missing data = 1		
Rhinorrhea		
Minor	88	39.46
Moderate	61	27.35
Important	43	19.28
Absent	31	13.90
Missing data = 1		
Sneezing		
Rare	94	42.73
Absent	55	25.00
Frequent no crisis	37	16.82
Frequent crisis	34	15.45
Missing data = 4		

NP's size-staging relationship with asthma, FDS and nasal symptoms

Thirty-six patients (16.07%) had stage I NP and 188 (83.93%) had large polyps stages II and III.

Asthma was found in 46.66% patients with NP stages II + IIII and in 20% patients with stage I nasal polyps. This difference was significant (χ^2= 0.0123).
The same tendency was found for FDS history: 35.36% in stages II+III and 11.76% in stage I of the NP (fisher p=0.0023).
More NHR history was found in patients with stage I NP (94.40%), than in patients with stages II and III (80.75%) but this difference was not significant (fisher p=0.15).
Major nasal obstruction was found in 82% of patients with stages II+III NP and in 61% of patients with stage I NP.
Nasal discharge was more frequent in stage I (97%), than in stages II+III (84%), but the difference was not relevant. The same was found for sneezing: 88% in stage I and 72% in stages II+III.
A significant difference was found for the smell loss. Smell was normal in 33% of patients with stage I and in only 7.5% of patients with stages II +II nasal polyps (χ^2<0.0001).

Sex relationship with asthma, NHR and FDS
More females had NHR (91.46% vs. 78.26%), asthma (46.84% vs. 40.60%), and FDS (42.86% vs. 24,44%) than males (Figure 1). The difference was significant for NHR (fisher p=0.0108) and for FDS (χ^2=0.0201).

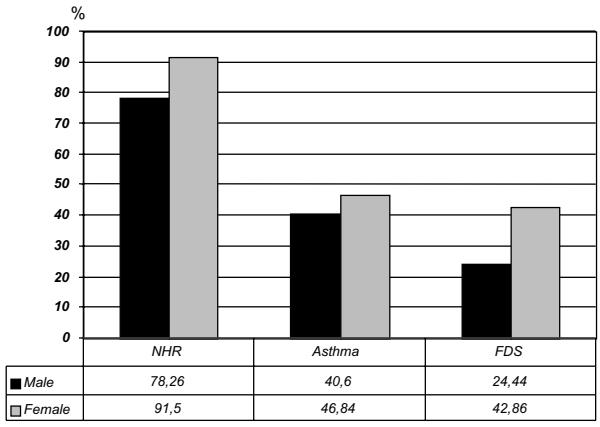

Figure 1. Sex distribution of patients with NHR, asthma and FDS.

DISCUSSION

Sex distribution, NP and associated conditions
Male patients were predominant in our study (63%) and this percentage is significantly higher (p<0.001) compared with the male percentage in the general population of France (48.7%). We wanted to know whether the sex distribution in this study was representative for the NP population or was affected by the sex distribution of patients regularly consulting in ENT. Total number of patients requiring medical consultation for any ENT pathology between 1991 and 1996 in one of the departments participating in this study was 13,583 with 63.7% women and 36.3% men. Thus, there is an inverse sex distribution of patients consulting in ENT for all pathologies comparing to patients presenting NP and enrolled in this study. Therefore, NP really seems to occur more often in men than in women.
However, we found more NHR, asthma and FDS in women than in men and the difference was significant for NHR and FDS. Thus, women suffering from NP appeared to be in a more severe condition than men. The same tendency was found by Larsen in his meta-analysis (Larsen, 1996).

Environment and smoking
No significant difference was found in terms of habitat and pollution at work. According to our study, these factors do not interfere with the natural history of the NP.
We found 15.45% smokers among patients enrolled in our study. If we compare with data provided by the French Department of Health (Baudier et al., 1998) concerning smokers in the general French population between 1992 and 1995 (35%), the difference is significant (p<0.001). Thus, NP seems to be associated with a non-smoking behaviour. It would be interesting to know how many of the non-smoking patients in our study were former smokers and if they stopped smoking when NP symptoms declared. Unfortunately, these points were not considered at the moment of data assessment.

Rhinologic Symptoms
Main symptoms of NP were bilateral nasal congestion and smell loss. The severity of these symptoms was directly correlated with the size of the polyp, as described in the literature (Hosemann et al., 1994; Lund, 1995). Moderate and important rhinorrhea was found in 46.63% of patients and frequent sneezing in 32.27%. These symptoms were slightly more frequent in patients with incipient NP, but the difference was not significant. Nevertheless, other authors (Braun et al., 1992) also reported more NHR in the early stages of the NP.
In the majority of cases, the onset of NP was insidious and nasal congestion and NHR were the first symptoms to occur. These symptoms progressively worsened in time according to 57% of our patients. Smell loss was less affected in the early phases of the NP and seamed strongly correlated (χ^2<0.0001) with the size of the polyps. Smell was normal in 33% of patients with small polyposis (stage I) and only in 7.5% of patients with large nasal polyps (stages II and III).

Asthma and FDS
A large number of our patients (100/224 i.e. 45%) had asthma. Within this group, asthma symptoms occurred rather before (43%), than after (21%), or simultaneously (30%) with the NP symptoms. Nevertheless, patients with incipient NP and no bronchial symptoms might be susceptible to develop asthma later since we found in our study twice as many asthmatics in patients with large NP (46%) than in the group of patients with small nasal polyps (20%). This difference was, of course, significant (χ^2< 0.0123).
FDS history was found in 31% of our patients. Among them,

64% reported asthma crisis mainly after ingestion of aspirin. However, patients must be questioned regarding the ingestion of champagne, white wine, whisky or other aperitifs containing sulfites susceptible to induce idiosyncratic reactions like nasal congestion, sneezing, headache (12% FDS patients in our study) or even asthma crisis (Arai et al., 1998; Vally et al., 1999). According to some authors (Lund, 1995; Larsen, 1996) FDS seems to occur more frequently in women than in men. Our study confirms this tendency since we found that about 43% of women had FDS versus 24.4% of men.

The family history of NP, asthma and FDS – a hereditary transmission?

Heredity has already been suggested as an etiological factor of NP. Greisner and Settipane (1996) studied the family history of NP in 50 adult patients with nasal polyps and found it positive in 7 cases (14%). Meanwhile, no family history of NP was found in their control group of patients.

The same was observed by Pialoux et al. (1999) in a pediatric population with NP (cystic fibrosis and primary ciliary dyskinesia-free).

In our study, positive family history of NP was found in more than half of patients (52.66%). Only reliable answers were considered (NP diagnosed by an ENT practitioner, or history of polypectomies and/or ethmoidectomy for NP). Seventeen /150 patients (11.33%) had two or more family members with NP. One patient had 4 and another had 7 family members with NP. Family history of asthma was found in 43,58% and the scores for anosmiant NHR, non-anosmiant NHR and FDS were respectively 23.77%, 29% and 12.21%. There is a meaningful difference if comparing with the family history of infectious chronic bronchitis which was found to be positive only in 4.24% of our patients.

These results are strongly suggestive of the existence of a hereditary factor in NP pathogenesis. A significant correlation between certain HLA alleles and nasal polyposis was recently pointed out. Luxenberger et al. (2000) found that HLA-A74 was frequently expressed in NP patients. Molnar-Gabor et al. (2000) showed that subjects carrying HLA-DR7-DQA1*0201, and -DQB1*0202 haplotype had 2 to 3 times higher odds ratios for developing NP than controls, and patients with Fernand-Widal syndrome (NP-asthma-FDS) carried the DR7 alleles significantly more often. Yet, there is no matching regarding the HLA patterns between these two studies and the results need to be confirmed by further research.

CONCLUSION

This study confirms that nasal polyposis is a chronic inflammatory disease frequently associated with asthma and with aspirin-like sensitivity. Asthma may occur years before the onset of the nasal symptoms. NP incidence seems significantly higher in the male that in the female population. However, females with NP appear to be in a more severe condition than men. These woman have a higher tendency to develop asthma and FDS. Hereditary factors might be considered and findings in our study lead us to further investigate the genetic factors that could be involved in this pathology.

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