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Nasal polyposis: is there an inheritance pattern? A single family study*

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SUMMARY

Background: *Nasal Polyposis (NP) is defined as a chronic inflammatory disease of sinonasal mucosa leading to diffuse formation of benign polyps. Although family histories are frequently suggested in medical literature, no specific study focused on this point has been reported. The purpose of this study is to determine whether a hereditary factor could be implied for NP in a family where several members were affected. We included 99 members of this family.*

Methods: *All patients were assessed for conditions known to be associated with the development or presence of NP. Concerning NP, patients were screened with a validated questionnaire and selected patients had a medical examination by an Ear, Nose and Throat practitioner.*

Results: *Thirteen patients had a personal history of NP without asthma, aspirin intolerance, Churg Strauss syndrome, cystic fibrosis, Young's syndrome, bare lymphocyte syndrome, or primary ciliary dyskinesia. Within this family, 19.7% of those older than 17 years were affected by NP, as compared with the national French prevalence of 2.1%.*

Conclusions: *Regarding the pedigree, we discuss different modes of inheritance. The presence of consanguineous unions in this family suggests the possibility of a common ancestor and thus a recessive autosomal mode of inheritance.*

Key words: nasal polyposis, genetic, heredity, risk factor, common ancestor

INTRODUCTION

Nasal Polyposis (NP) is defined as a chronic inflammatory disease of nasal and sinus mucosa leading to diffuse formation of benign polyps protruding from sinuses into the nasal cavity [1-3]. Recently, there have been some advances in understanding the role of cellular and molecular factors in the physiopathology of the NP [4-9]. Although nasal polyps are a common clinical finding and occur in between 0.5% to 4% of the population, little is known about their etiology [10-15]. The difference in prevalence reported is related to the different methods used inthese studies (questionnaire, nasal endoscopy). A recent study based on a population questionnaire revealed a prevalence of 2.1% in France [13]. Sex ratio remains uncertain. However, it seems that males are more often affected [4,16,17]. NP was found most commonly in those older than 40 years [2,18], while people undergoing surgery tend to be over 50 years old [1].

Some conditions are known to be associated with the development of NP [1]: Cystic fibrosis (OMIM 219700), Young's syndrome (OMIM 279000), Churg Strauss syndrome, bare lymphocyte syndrome (OMIM 209920), or primary ciliary dyskinesia (OMIM 242650). Other pathological conditions frequently reported are asthma (30-70%), aspirin intolerance (13-25%) or both [2,19]. Nevertheless, some patients with NP don't have any associated pathology.

To our knowledge although family histories are frequently suggested in medical literature, no specific family study has been reported [17,20,21]. The rationale for the present study was to analyze in a family of several generations with two consanguineous unions, the presence of isolated nasal polyposis in order to assess its potential mode of genetic transmission.

MATERIALS AND METHODS

Study Design

The clinical study went on from October 2004 to March 2005. As we noticed many affected members of NP in this family with two consanguineous unions, we hypothesized a genetic factor could be implied and screened each member for the presence of NP.

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Population

Patients belong to a single family originating from a little town of less than 3500 inhabitants in the west of France.

Diagnosis of NP

NP diagnosis was made either after medical examination including nasal endoscopy or through direct interview using a diagnostic questionnaire validated in a large population in France (specificity 88%, sensitivity 89%) [22]. The questions were written in layperson language in order to ensure maximal comprehension and optimize the rate of response. Depending of their place of residence, patients who were selected through the questionnaire were subsequently examined by an ENT practitioner from a national university hospital to document the presence or absence of NP.

The Stage of nasal polyps was noted for each person and each side. We used the classification from EPOS 2007 [2]:
Stage I: Polyps in middle meatus
Stage II: Polyps beyond middle meatus but not blocking the nose completely
Stage III: Polyps completely obstructing the nose

A systematic nasal endoscopy of every member of the family would have reinforced the quality of the study, but considering their large number and their different locations in France, it was practically impossible.

Comorbidity

Patients with NP were asked about symptoms of asthma, aspirin intolerance, Churg Strauss syndrome, Cystic fibrosis, Young's syndrome, bare lymphocyte syndrome or primary ciliary dyskinesia. To rule out cystic fibrosis in NP patients a sweat test was performed for all patients with a medical follow up in our institution (n=9). Moreover we looked for mutations in the CFTR gene in a severely affected patient of the family who has 5 sisters and 1 brother affected with NP. An extensive search for mutations was performed on leucocyte DNA obtained from blood, by methods combining Denaturing Gradient Gel Electrophoresis (DGGE) and Denaturing High Performance Liquid Chromatography (DHPLC) of all exons of the CFTR gene, as well as quantitative PCR methods assessing intragenic rearrangements. Skin prick tests for common allergens were done for all patients followed up in our institution.

Pedigree

A pedigree was drawn after analysis of all collected data. For each individual, the roman numeral indicates his generation and the arabic numeral his place in the generation. Some people have a bis number as they were discovered subsequently. For future genetic research, the oldest generation was designated by the roman numeral III.

RESULTS

Population

Ninety-nine people were included in the study.
The distribution includes 4 generations with respectively 2 persons in the first and oldest generation (called generation III), 17 persons in the second generation (called IV), 33 in the third generation (called V), and 47 in the last and youngest generation (called VI) (Figure1). Most of the 99 persons had blood ties (95/99). Some persons without blood ties were chosen because they were married with members of the family (for the genetic research). At the date of the study, 94 of the family were still alive. Twelve living people were already known to have NP. All the other living people accepted to answer to the medical questionnaire when possible (the limit was only the age of understanding). The 5 dead persons were presumed to be NP free.

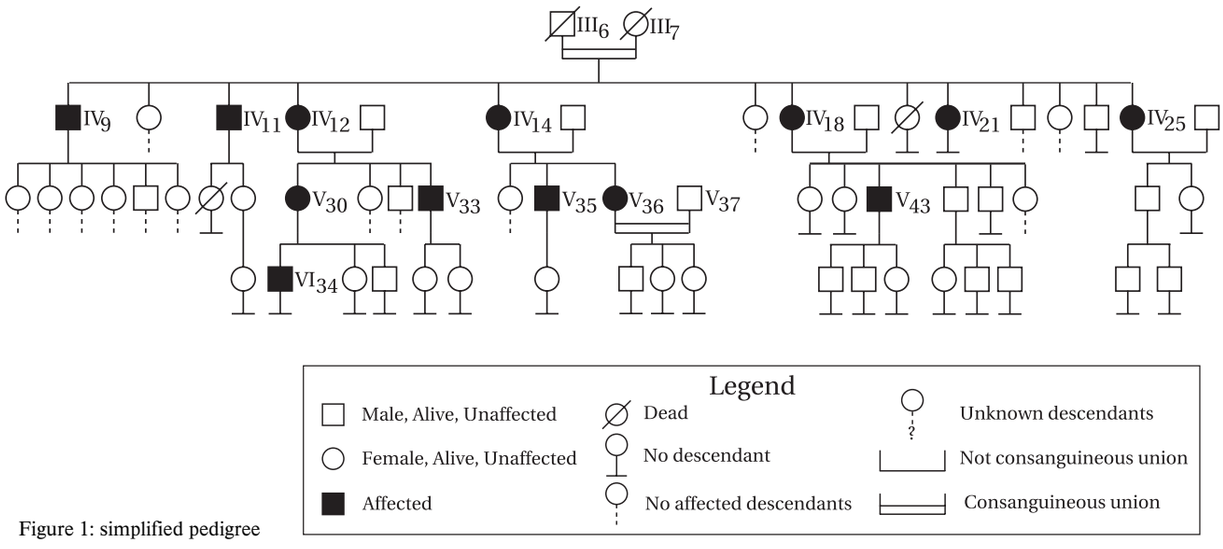

Figure 1: simplified pedigree

Table 1. Characteristics of Patients with NP.

Patient	Sex	Stage of nasal polyposis on the right side	Stage of nasal polyposis on the left side	From consanguineous union	Age at diagnosis	Dead or alive
IV 9	m	III	III	yes	60	a
IV 11	m	III	III	yes	18	a
IV 12	f	III	III	yes	18	a
IV 14	f	III	III	yes	12	a
IV 18	f	III	III	yes	14	a
IV 21	f	I	Oedema	yes	55	a
IV 25	f	III	III	yes	14	a
V 30	f	II	II	no	20	a
V 33	m	I	II	no	43	a
V 35	m	III	III	no	33	a
V 36	f	II	II	no	34	a
V 43	m	II	I	no	32	a
VI 34	m	I	Oedema	no	18	a

The sex distribution in the global population (n=99) was:
- 54 males (1 in generation III, 8 in generation IV, 16 in generation V, 29 in generation VI)
- 45 females (1 in generation III, 9 in generation IV, 17 in generation V, 18 in generation VI)

The age distribution at the end of the study among the living people (n=94) was:
- 33: seventeen years old or less (all in generation VI).
- 61: eighteen years old or more

The 5 dead persons were 18 years old or more at the time of death.
If we consider only those 18 years old or more who were alive at the time of study (n=61), 12 were already known to have NP before the study and 49 accepted to answer to the medical questionnaire. Among the 49 people who answered the medical questionnaire, 5 were identified as potential NP patients on the basis of their answers. Among these 5 persons, medical examination revealed that 4 were NP free (IV22, IV25, V38, V39) and 1 had NP (V33).

At the end of the study, 13 NP were recruited (all over 18 years old) (Table 1):
- 12 were already known before the beginning of the study
- 1 was confirmed by nasal endoscopy after a positive questionnaire.

All patients with NP were alive and aged of 18 years or more in March 2005. They were divided up among four generations. The 13 patients consisted of 6 men and 7 women with an average age at diagnosis of 28.5 years (12 – 60 years). Seven patients were born from consanguineous union (53.8%). The degree of consanguinity of the unions is 1/16 for III6 and III7 and 1/256 for V36 and V37. The stages of NP are shown in Table 1. Two people, IV21 and VI 34, had only mucosal oedema on one side. A bilateral III stage was found in 7/14 affected people.

Occurrence of NP in the total adult population (> 18 years) was 19.7 % (13/66). We selected 18 years old as the cut-off point to compare the prevalence of nasal polyposis in this family because in the majority of previous publications, the prevalence is given for the adult population over 18, and except for cystic fibrosis and primary ciliary dyskinesia, nasal polyposis is mainly discovered in adults.

Associated pathologies: No patient with NP of this family had symptoms of Churg Strauss syndrome, Cystic fibrosis, Young's syndrome, bare lymphocyte syndrome or primary ciliary dyskinesia. No patient had asthma, and only one had aspirin intolerance (IV18) after specific medical investigation. Allergy was absent for the 9 patients with a medical follow-up in our institution (after skin prick test for common allergen). The sweat test was also negative for those nine patients. Concerning the CFTR gene mutation research, the IV 11 was chosen as both the patients, his brother and his five sisters had NP. This man is severely affected by NP (Table 1). He was free of more than 92% CF mutations (detailed tests including research of intragenic variations).

PEDIGREE

Ninety-nine persons were included in the family's pedigree. In this family, two unions were consanguineous but some others were between males and females native from the same small town. We selected part of this pedigree with many affected members for a genetic study, which is still on going, and pictured it (Figure 1).

DISCUSSION

The aim of this work was to explore a possible mode of hereditary transmission of NP within a same family. Currently, there is no established mode of inheritance for NP except when it is part of a genetic disease such as cystic fibrosis [23]. NP is generally considered as a multi factorial disease where environmental factors can influence or cause an inflammatory reaction [2,

[24]. Whether this inflammatory reaction is determined genetically is unknown. Karjalainen suggested a role for the gene encoding IL-1A and Yea found in the Korean population that polymorphism of IL-4 was associated with a protective mechanism against NP [25,26]. Familial history of nasal polyposis is frequently observed in several publications [17,20,21,27]. Rugina found a positive family history in more than half of 224 patients [17]. A lower percentage (14%) was reported by Greisner [20]. The ORLI group experience describes 52.66 % [18] of cases with familial history of NP and Braun 40% [27] but without real analysis of the family in each case.

Furthemore, significant correlations between certain HLA (human leukocyte antigen) and NP have been recently noted. Molnar-Gabor also reported that patients carrying HLA-DR7-DQA1*0201 and HLA-DR7-DQB1*0202 haplotype develop more frequently nasal polyps [28]. Luxenberger found a significant association between HLA-A74 and nasal polyps despite the fact that this haplotype is very uncommon [29]. The risk of developing NP can be 5.53 times higher in subjects with HLA-DQA1*0201-DQB1*0201 haplotype [30]. Such susceptibility to develop NP may be influenced by ethnicity as shown by Ramirez-Anguiano in the Mexican Mestizo population where an increased frequency of the HLA-DRB1*03 and HLA-DRB1*04 allele was found [31]. Two recent studies about gene expression profiles in NP tissues compared to control mucosa have shown differential expression with up regulated or down regulated genes [32,33].

The family we described includes 4 generations in which 3 generations have a total of 13 cases of NP. The diagnostic questionnaire made it possible to identify one patient who did not know he had NP among five people with a positive questionnaire – the diagnosis was confirmed for this man (V33) through endoscopy. This result (1/5) is not in accordance with the specificity and specificity described for this questionnaire (respectively 88% and 89%) [22] however, our positive sample consisted of only five people. However, the shortcomings of this test suggest that we may have missed some cases with polyps – something that would have reinforced the inheritance pattern. However, the presence of further, asymptomatic patients is unlikely, as most of cases with polyps in this family presented with a massive and diffuse nasal polyposis (75%). In this family, with only people aged over 17 years old, 19.7 % are affected by NP, whereas 2.1% are affected in the general population [13]. To our knowledge, the largest family reported before included just 4 cases [20]. In these publications, no description of consanguineous unions or information about the total number of members in the family were available. De Leng has recently reported a more frequent presence of NP in Peutz Jeghers syndrome with a familial history (autosomal dominant) [34]. Cohen confirmed through questionnaire the common presence of familial history in the most severe cases of NP. He suggested a correlation with disease severity as we found [35].We observed a gender preponderance (62.5% males) as shown previously [2,27]. Patients' average age of diagnosis was younger than previously reported (28.5 years) [2,27]. Three cases were diagnosed before they were 18 years old.
Among these patients with NP, after medical interview or functional pulmonary test, no asthma was found and aspirin intolerance was found in one case (7.7%). Thus, in this family, NP seems to be independent of other often associated diseases and implies genetic factors should be different from those implied in other diseases as cystic fibrosis, primary ciliary dyskinesia or asthma.

In this family, NP often occured during the end of adolescence, without asthma and aspirin intolerance, but with a severe course. Seven patients had bilateral stage III NP (Table 1).
A histological analysis was available for 7 patients who were operated. Lympho-plasmocytes were the main inflammatory cells in 6/7 cases as reported in cystic fibrosis. Eosinophils were rarely present in nasal polyps. This led us to suspect cystic fibrosis. However, cystic fibrosis was excluded by an extensive investigation of the mutations in the CFTR gene, by sequencing the whole gene and searching for intragenic rearrangements. This suggests that there may be a "genetic" form of nasal polyposis (excluding cystic fibrosis) in this family. The younger age of occurrence of NP and the more severe course, compared to sporadic NP, suggest a genetic causing factor. This is well known in breast or colon cancers for example where a young age of occurrence is strongly in favour of an inherited form of cancer [37].

Among the thirteen patients with NP, seven were born from consanguineous unions. The six others were born from unions between spouses' natives either from the same village or from a village less than thirty kilometers away (V33, V35, V36, V43, VI34). Moreover for five of them (V30, V33, V35, V36, V43) there was a familial link between their second relative (IV13, IV15, IV19). In this family, we think that the occurrence of the disease in 7 out the 13 children born from the union of their unaffected parents III6 and III7 is in favour of an autosomal recessive inheritance, since these 2 individuals are second cousins (high degree of consanguinity of 1/16). When looking to descendants of IV12, IV14 and IV 18, with affected children at generation V and VI, an autosomal dominant inheritance is possible, except if theirs spouses were heterozygous too, which would argue for a recessive mode. This could be the case, as theirs spouses are natives either from the same small village or from a village less than thirty kilometers away, which could be in favor of a common ancestor, even if there is no known consanguinity. For all these reasons, and also because of the younger age of onset of polyps as usually, even if a dominant inheritance cannot be ruled out, we think that an autosomal recessive is the more likely mode of inheritance in this family with the probability that all these patients have a common ancestor. Furthermore, the pedigree showed a "horizontal"

genetic transmission [seven children with NP from parents without NP (IV9, IV11, IV12, IV14, IV18, IV21, V25 and III6, III7)], which is rather characteristic of a recessive autosomal mode of inheritance like in cystic fibrosis for example. Patients with NP could be homozygous for a mutation in a putative gene. Parents of affected patients should be heterozygous healthy carriers for the mutation. This mutation could have been inherited from a common ancestor. Greisner did the same hypothesis with four cases in one family [20]. For the union between V36 and V37, the degree of consanguinity is low: 1/256. Their grand-grand parents were brother and sister. Medical geneticists suspect an autosomal recessive inheritance when there is a common ancestor, whatever the degree of consanguinity is. In this particular union, the fact that their children are unaffected does not disprove this type of inheritance. When two parents are heterozygous or healthy carrier for a mutation, the risk for each of their children to be affected is ¼.

Finally, when NP is part of a genetic disease, this disease is most often inherited with a recessive autosomal mode, as cystic fibrosis, primary ciliary dyskinesia, Young's syndrome or bare lymphocyte syndrome. Dominant autosomal transmission with incomplete penetrance cannot be ruled out but is unlikely because of the presentation of the pedigree and the consanguineous unions in this family. Although there is a slight male preponderance, X-linked transmission is unlikely because the disease is of equal intensity among affected males and females. Male preponderance has been reported before in sporadic cases. It could be explained by environmental factors.

CONCLUSION

This family with NP is remarkable by the number of affected individuals and the consanguineous unions, and the fact that NP is not associated with other conditions that are known to be of genetic origin, such as cystic fibrosis. This study led us to think about the eventual presence of genetic predisposition of nasal polyps. In the adult members of this family, the prevalence of NP was 19.7%, whereas only 2.1% of the French population are affected in the [13]. In this family, a recessive autosomal pattern is the more likely mode of inheritance. There is probably a common ancestor who had a single gene mutation that was associated with this condition. The clinical study is over. Blood samples for DNA analyse have been taken from more than 40 affected and unaffected members of the family for a linkage analysis. On the basis of the hypothesis of a recessive autosomal transmission, a genetic investigation, aiming to localize a gene is going on. Finding other such families in the world would be of great interest, as this kind of analysis on only one family is very difficult and it would be very helpful to be able to analyse other such families. One or several genes could thus be identified. That would make it possible to improve comprehension of the physiopathology of the disease that could perhaps explain even the sporadic cases of NP.

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