ORIGINAL CONTRIBUTION

Rhinology 49: 347-355, 2011

# Nasal polyposis and cystic fibrosis (CF): review of the literature *

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SUMMARY

*The aim of this study was to address whether NP might be a predictive factor for severity of CF. The authors collected data from the literature on NP as a unique or associated sign in CF and reviewed the clinical and molecular aspects of CF associated with NP. CF genotypes and clinical severity in NP(+) vs. NP(-) patients were reviewed, taking into account pulmonary function, frequency of P. aeruginosa lung infection, frequency of allergy, nutritional status, and exocrine pancreatic function. The CFTR gene was also analyzed in a patient with isolated severe NP as the unique feature of CF. This review of the literature showed a 'milder' phenotype in 'NP+' vs. 'NP-' CF patients, contrasting with a marked association between NP and 'severe' CF mutations. In addition, a complex genotype was identified, associating four heterozygous variants, namely p.Q493X (a severe mutation) on the paternal allele, and p.V562I, p.A1006E, and (TG)11(T)5 (IVS8-5T) on the maternal allele, in a case of CF presenting as isolated NP. The authors speculate that genetic/environmental factors associated with NP might attenuate the functional impact of 'severe' CF mutations. The overrepresentation of CF carriers among patients with isolated NP also advocates the need for CFTR molecular screening in such populations for genetic counselling purposes.*

*Key words: cystic fibrosis, CFTR, nasal polyposis, CFTR mutations, genotype-phenotype relationship*

## INTRODUCTION

The prevalence of nasal polyposis (NP) has been estimated to be 6-48% in several series of patients with cystic fibrosis (CF) [1-7], and as high as 53 and 57% in two pediatric series [8,9]. Some reports have suggested that CF patients with NP present milder pulmonary disease, with a lower age at diagnosis, and improved survival, compared to CF patients without NP [1]. However, most of these reports were based on small sample sizes with imprecise or incomplete phenotype/genotype data, thereby precluding any definite conclusions on this point.

NP has also been reported to be an isolated feature of CF in extremely rare cases, in which patients were shown to suffer from CF only on the basis of elevated sweat chloride levels. It is not known whether such an unusual CF phenotype might be promoted by particular CF mutations.

Data were collected from published reports comparing CF patients with or without NP, to evaluate whether NP might be associated with a lower severity of CF and a different pattern of CF mutations, compared to NP-free CF patients. We also report a novel case of isolated NP in a CF patient harboring a complex CF genotype.

## METHODS

### *Literature*

Review of the literature was restricted to reports indexed in the Pubmed site (keywords: NP, CF, CF mutations) between 1992 and 2008, and including at least 20 CF patients with clearly defined NP(+)/NP(-) status and CF mutation analysis. Parameters taken into account in this review were CF genotype and clinical status, such as lung function capacities (forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC)), *P. aeruginosa* pulmonary infection, pancreatic and nutritional status (height and weight, gastrointestinal status),

*Received for publication: September 21, 2010; accepted: January 9, 2011

DOI:10.4193/Rhino10.225

and allergy (skin prick test).

*Statistics*
Statistical data (Tables 1-3) were either drawn from the reports analyzed in this review, or performed with the Chi-square test.

*Case report*
The patient, a male from Southern France, currently aged 26 years, was initially referred to Necker-Enfants Malades hospital at the age of 10 with massive severe nasal polyposis requiring three surgical procedures at the ages of 12, 15, and 20 years. CF diagnosis was based on repeated positive sweat chloride values (≥ 70 mmol/L). Nasal polyposis was and remains the only symptom of CF: in particular, no pulmonary or intestinal clinical features were observed in this pancreatic sufficient patient.

*DNA analysis*
Informed consent for DNA analysis was obtained from the patient and his parents. DNA was extracted from peripheral blood leukocytes. The 27 exons and flanking intronic splice junctions of the CFTR gene (Genbank NC_00007) were scanned, using either a combination of denaturing gradient gel electrophoresis (DGGE) [10] and sequencing for exons 3-5, 7, 11-14, 17b-21, or direct sequencing for exons 1-2, 6, 8-10, 15-17a, 22-24, using an automated ABI prism 310 DNA sequencer (Applied Biosystems, France) as previously published [11]. CF gene variants detected in the patient were subsequently searched in his parents. Nomenclature was defined according to the CF mutation database (http://www.genet.sickkids.on.ca/cftr).

RESULTS
Review of the literature was based on 12 studies [1-9,12-14] including 1,218 NP(+) CF patients and 20,038 NP(-) CF patients. These studies included children [5,6,8,9], adults [3,7], and both children and adults [1,2,4,12-14]. Seven studies compared NP(+)/NP(-) patients [1-7]. While NP was observed in 32% to 44% of CF patients in most reports (ranging from 39 to 211 CF patients) [2-7], NP prevalence fell to 4% in a large CF patient database (815 NP out of 20,198 CF patients [1]. Five studies described only NP(+) CF patients [8,9,12-14].

This review was designed to: 1) compare disease severity [1-7] 'Table 1' and CF genotype [1,2,4,5,12] 'Table 2, 3' in NP(+) vs. NP(-) patients and 2) describe the various grades of severity of nasal polyps within the NP(+) population [8,9,13,14].

***NP(+) vs. NP(-) CF patients***
*Clinical data (Table 1)*
Compared to NP(-) CF patients, NP(+) patients 1) presented a balanced male:female sex ratio in one large study [1] of the three studies that reported patient gender [1,5,6], while the small sample size of the remaining 2 series precluded any conclusions. 2) appeared to be younger at CF diagnosis in the only series [1] that reported this parameter, (2.5 vs. 2.9 years among NP(+) and NP(-), respectively), and 3) had similar chloride sweat test values in the two studies that reported these data [1,5].

Pulmonary function data were reported in 7 out of 12 studies (Table 1) [1-7]. Better pulmonary function was observed in NP(+) vs. NP(-) CF patients in 4 studies [1,2,5,6], based either on FEV1 and FVC [1,5,6], or an imprecise clinical score [2], while 3 other studies failed to detect any difference between the two groups [3,4,7].

Lung infection was reported in 4 studies [1,2,4,5]. Three of these studies [1,4,5] showed a significant excess of *P. aeruginosa* chronic colonization, and two of these three studies also showed a higher frequency of acute exacerbation, and hospitalisation per year. Accordingly, a longer duration of *P. aeruginosa* colonization was observed in NP(+) (n = 45, 10 yrs ± 6.9) vs. NP(-) (n = 68, 5.8 yrs ± 4.4) subsets in one study [4], resulting in a correlation between early *P. aeruginosa* chronic colonization in the lower respiratory tract and nasal polyps.

In 3 [1,2,5] out of 7 studies [1-7], NP tended to be associated with 1) a better nutritional status, as reflected by higher weight and height values in 2 (1.5) out of 3 studies [1,2,5] 2) a lower incidence of gastroesophageal reflux [2], or 3) milder gastrointestinal symptoms in infancy [1,2]. One study did not report any difference between the two groups [6], and the remaining three studies did not report the nutritional impact [3,4,7].

A higher frequency of allergy in the NP(+) subset, with positive skin prick test to *Aspergillus fumigatus* (37% in NP(+) vs. 21% in NP(-), ($p < 0.01$)) was observed in 1 [5] of the 3 reports [3-5]. Allergic problems in NP(+) were not more frequent than the allergic problems in the NP(-) CF group reported in the other two series (21% vs. 33%, respectively, p = NS [4], 41% vs. 39% respectively, p = NS [3]).

*Mutation analysis (Table 2)*
Five of the 12 studies were selected for this analysis [1,2,4,5,12] based on the availability of genotype and NP(+)/NP(-) comparative data. Three groups were taken into account, namely, F508del, non-F508del, and unknown mutations. A total of 44 CF mutations were identified: 27 were considered to be 'severe' and 17 were considered to be 'mild'. The frequency of the prevalent F508del mutation was similar in NP(+) vs. NP(-) CF patients (69.6% vs. 68.4%, p = 0.47). The non-F508del subset of mutations was overrepresented in the presence of NP (9.1% vs. 6.5%, p = 0.003). When the non-F508del mutation group was divided in two subsets, namely 'severe' and 'mild' mutations, the number of mutations identified in each group was too small to analyze differences between NP(+) and NP(-) groups, except for the 3272-26A>G mutation, described in one study [12], that was significantly associated with the presence of NP (38% in NP(+) vs. 17% in NP(-) patients, p = 0.002).

*Genotype analysis (Table 3)*
The frequency of F508del homozygosity, F508del com-

pound heterozygosity, and non-F508del genotypes was similar between NP(+) and NP(-) CF patients (p = 0.89). Only F508del/G551D compound heterozygosity was reported as being significantly more frequent in the NP(+) group (12.1% vs. 7.1%, p = 0.05) in Kingdom's large series [1]. The small sample size of the remaining series [2,4,5,12] precluded any clear conclusions on genotype distribution. However, the prevalence of nasal polyps was significantly higher in compound heterozygotes for 3272-26A>G (intron 17a), and a second 'trans ' mutation (F508del or another severe mutation) than in the F508del homozygous group, in a report on 119 CF patients (37% vs. 8.8%, respectively) [12]. The significant number of non-identified mutations in all reports precluded any attempt at correlating the presence/absence of NP with the presence of 0, 1, or 2 severe mutations.

*NP severity in CF patients*

Four studies reported clinical phenotypes according to the grade of polyps [8,9,13,14], or the site of the disease, ie unilateral or bilateral disease [8,14]. The classification of NP based on nasal endoscope examination was performed according to the classification proposed by Mackay and Lund [16]; i.e.

Table 1. Nasal polyposis (NP) in association with "typical" CF: review of the literature.

| CF individuals | | | Clinical condition in NP(+) vs. NP(-) patients* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| number | age | NP frequency (%) | Allergy frequency | PI | lung injury | | P.A. colonisation | nutritional impact | | references |
| | | | | | FEV1 | FVC | | Height | Weight | |
| 39 | A | 44 | | → | → | | | | | Kerrebijn [7] |
| 66 | A+C | 32 | | → | | | 61% vs.75% → (NS) | | © ↘ | De Gaudemar [2] |
| 20198 | A+C | 4 | | → | 75% vs. 69% p<0.001 ↘ | 86% vs.82% ↘ | 64% vs. 58% p<0.01 ↗ | (d) 34% vs. 32% p<0.03 ↘ | (d) 31% vs. 27% p<0.001 ↘ | Kingdom [1] |
| 211 | A | 37 | → 41% vs. 39% | → | | | | | | Hadfield [3] |
| 111 | A+C | 39 | → 21% vs.33% | → | 75±24% vs. 78±26% → | | (b) p=0.0001 ↗ | | | Henriksson [4] |
| 89 | C | 33 | (a) ↗ 37% vs. 21% | → | 73±16% vs. 67±13% ↘ | | 51% vs. 36% p<0.01 ↗ | 37±28% vs. 31±26% ↘ | 42±29% vs. 38±24% ↘ | Cimmino [5] |
| 140 | C | 40 | | | 84% vs.79% ↘ | 89% vs.83% ↘ | | 97% vs.97% → | 96% vs. 96% → | Slieker [6] |

A: adults, C: children < 16 years, NP: nasal polyposis, PI: pancreatic insufficiency, PA: *P. aeruginosa,* *: criteria for assessment of clinical condition: age at onset, Schwachman score (15), pulmonary function tests (FEV1, FVC), need for pancreatic enzyme supplement, number of courses of antibiotic per year, bone mineral density (BMD), skin prick test. a) A*spergillus fumigatus*, b) sputum or *P. aeruginosa* antibody titer, c) gastroesophageal reflux, d) NHCS: National Central of Health Statistics score (% predictive). Empty space: unspecified features. When available, in study report, p values and data are given.

Higher ↗, similar →, lower ↘, in NP+ vs. NP- patients.

Table 2. Frequency of F508del and non-F508del mutations in NP(+) versus NP(-) CF patients.

| | | NP(+) | | | | | | | NP(-) | | | | | | | p | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CF alleles | Kingdom[1] | Cimmino[5] | De Gaudemar[2] | Henriksson[4] | Amaral[12] | total alleles | % | Kingdom[1] | Cimmino[5] | De Gaudemar[2] | Henriksson[4] | Amaral[12] | total alleles | % | total | study[1] |
| A) | F508del | 469a (74.4%) | 27 | 28 | 50 | 26 | **600** | **69.6** | 9233a (68.5%) | 62 | 63 | 72 | 147 | **9577** | **68.4** | 0.47 | 0.002 |
| | I507del | 2 | * | * | | | | 0.3 | 17 | * | * | | | | 0.1 | | |
| B) | E60X | | * | | | | | | | * | | | | | | | |
| | 297-3C>A | | | | * | | | | | | | * | | | | | |
| | 394delTT | | * | | * | | | | | * | | * | | | | | |
| | 621+1G>T | 2 | * | * | | | | 0.3 | 59 | * | * | | | | 0.4 | | |
| | 711+3A>G | | | | * | | | | | | | * | | | | | |
| | 711+5G>A | | * | | | | | | | * | | | | | | | |
| | Y122X | | | * | | | | | | | * | | | | | | |
| | 1717-1G>A | 1 | 1 | * | | * | | 0.3 | 57 | 1 | * | | * | | 0.4 | | |
| | W846X | | | | | * | | | | | | | * | | | | |
| | S549R | | | * | | | | | | | * | | | | | | |
| | G542X | 3 | 2 | * | | * | | **0.7** | 188 | 2 | * | | * | | **1.4** | | |
| | G551D | 13 | * | * | * | | | **1.9** | 195 | * | * | * | | | **1.4** | | |
| | Q552X | | * | | | | | | | * | | | | | | | |
| | R553X | 6 | * | * | * | | | 0.9 | 76 | * | * | * | | | 0.5 | | |
| severe | 2143delT | | * | | | | | | | * | | | | | | | |
| | 2183delAA | | 1 | | * | | | | | * | | * | | | | | |
| | 2184delA | | * | | | | | | | * | | | | | | | |
| | E822X | | | | | * | | | | | | | * | | | | |
| | 2789+5G>A | | * | | * | | | | | * | | * | | | | | |
| | 2869insG | | | | | * | | | | | | | * | | | | |
| | R1158X | | * | | | | | | | * | | | | | | | |
| | R1162X | 1 | * | * | | * | | 0.1 | 8 | * | * | | * | | 0.05 | | |
| | 3659delC | | * | * | * | | | | | * | * | * | | | | | |
| | 3849+10kbC>T | 3 | * | | | | | 0.4 | 40 | * | | | | | 0.3 | | |
| | W1282X | 5 | 1 | * | * | * | | 0.9 | 88 | 1 | * | * | * | | 0.6 | | |
| | N1303K | 6 | 2 | * | | * | | 1.1 | 120 | 4 | * | | * | | 0.9 | | |
| | 3905insT | | * | * | | | | | | * | * | | | | | | |
| | 4016insT | | * | | | | | | | * | | | | | | | |
| | 4218insT | | | | | * | | | | | | | * | | | | |

grade 0: asymptomatic, 1: small polyps in middle meatus, mild symptoms, 2: NP localized in middle meatus, reaching inferior border of middle turbinate, 3: extending into the whole nasal cavity below the edge of the middle turbinate, requiring surgery and 4: filling up the whole nasal cavity with obstruction, requiring surgery.

Genotypes were reported in 3 studies [9,13,14]. The small number of patients and the small number of CF mutations tested in 2 of the 3 reports precluded any attempt to establish genotype/phenotype correlations [9,14]. One study [13] showed a significant association between the grade of severity of polyps (44 NP and 19 ethmoidal polyps) and F508del homozygosity, that was significantly more frequent in NP class 3 requiring surgery than in class 0 (79% vs. 38%, respectively, $p < 0.02$), suggesting a risk factor for serious sinus disease related to F508del homozygosity.

*Case report*

We found a patient with NP as an isolated feature of CF. A complex genotype comprising four heterozygous variants was identified in this patient (Table 4). The c.1609C>T mutation (p.Q493X, exon 10), with a paternal origin, is a severe mutation supposed to result in either mRNA decay or CFTR truncation by 987 aminoacids. The maternal allele included 3 sequence variants, i.e., c.1816G>A in exon 12 (p.V562I), c.3149C>A in exon 17a (p.A1006E), and c.1342-34(TG)11(T)5 (IVS8-5T). Each variant has been previously reported in association with typical or atypical forms of CF. Two neutral polymorphisms were present in a homozygous state in exons 14 and 24, namely c.2694T>G (p.T854T) and c.4521G>A (p.Q1463Q), located in TD2 and C terminal domains, respectively (Table 5).

| | | NP(+) | | | | | | | NP(-) | | | | | | | p | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CF alleles | Kingdom[1] | Cimmino[5] | De Gaudemar[2] | Henriksson[4] | Amaral[12] | total alleles | % | Kingdom[1] | Cimmino[5] | De Gaudemar[2] | Henriksson[4] | Amaral[12] | total alleles | % | total | study[1] |
| mild | R75Q | | | | * | | | | | | | * | | | | | |
| | W79R | | | | * | | | | | | | * | | | | | |
| | G85E | | * | | | | | | | * | | | | | | | |
| | P99L | | | | | * | | | | | | | * | | | | |
| | Y109N | | | | * | | | | | | | * | | | | | |
| | R117H | | * | * | | | | | | * | * | | | | | | |
| | I148T | | * | | | | | | | * | | | | | | | |
| | L206W | | | | * | * | | | | | | * | * | | | | |
| | R334W | 2 | * | | | | | 0.3 | 11 | * | | | | | 0.08 | | |
| | R347P | | * | | | | | | | * | | | | | | | |
| | A455E | | * | | | | | | | * | | | | | | | |
| | R560T | | * | | | | | | | * | | | | | | | |
| | S945L | | | | * | | | | | | | * | | | | | |
| | 3272-26A>G | | | | | 19♦♦ | | 38 | | | | | 32♦♦ | | 17 | | |
| | N1088D | | | | * | | | | | | | * | | | | | |
| | D1152H | | | | * | | | | | | | * | | | | | |
| | G1244E | | * | | * | | | | | * | | * | | | | | |
| | S1251N | | * | | | | | | | * | | | | | | | |
| | non-F508del mutations | 44 | 7 | 9 | | 19 | **79** | **9.1♦** | 859 | 8 | 15 | | 32 | **914** | **6.5♦** | 0.003 | 0.54 |
| | A + B | | | | | | **679** | **78.8** | | | | | | **10491** | **74.9** | | |
| **C)** | X | 117 | 24 | 5 | 32 | 5 | 183 | 21.2 | 3386 | 50 | 12 | 46 | 9 | 3503 | **25** | 0,012 | 0,0002 |
| | A + B + C | 630 | 58 | 42 | 82 | 50[b]♦♦ | 862 | | 13478 | 120 | 90 | 118 | 188[b]♦♦ | 13994 | | | |

A) a: p = 0.002, significant difference between NP(+)/NP(-) CF patients, NS: not significant, %: allelic frequency. B) *: mutations tested in the studies with no distinction of NP+ vs. NP- groups. ♦: p = 0.003, ♦♦: p = 0.002. C) X: unspecified mutation, b: data taking into account the only subset of patients in which genotype and the presence or absence of NP were reported.

## DISCUSSION

Nasal polyposis (NP) affects 1 to 4% of the general population worldwide [17]. Causes of this heterogeneous condition remain largely unknown, but a multifactorial contribution has been suggested [17], and a clear association has been reported with non-allergic respiratory disease (rhinitis and asthma) [18], aspirin sensitivity, and CF [19]. Accordingly, a recent genome-wide association study for chronic rhinosinusitis (CRS) in the Hutterite population [20] identified the 7q31.1 locus (including the CFTR locus) as a susceptibility marker for CRS.

The prevalence of NP in CF varies considerably, ranging from 32% to 44% in six series published to date (including 39 to 211 patients). The largest series (20,198 patients) reported a 4% prevalence exclusively in CF patients all affected with serious NP requiring surgery [1]. The results of most published studies could not be analyzed due to the lack of accurate data on phenotype traits or genotypes. However, in the current report, a comprehensive review of the literature suggested that NP-CF patients generally showed milder lung impairment [1,5,6], and better nutritional status [1,2,5], contrasting with the higher incidence of *P. aeruginosa* colonization [1,4,5], compared to NP-free CF patients.

Little is known about the pathophysiological bases accounting for the development of nasal polyps in CF. The development of NP could conceivably be at least partly dependent on the type and location of the CF mutation. We therefore listed all identified mutations in reports concerning patients with typical CF and NP. Most studies emphasized the frequency of F508del homozygosity in CF patients with NP. A high incidence of NP was also reported in patients carrying 3272-26A>G (a broad spectrum CF mutation in CFTR intron 17a), in 'trans' associated with F508del or another severe CF mutation [12]. However, a significant proportion of CF mutations was not identified in the CF series included in this review ('Table 2',

Table 3. Comparison of mutations and genotype frequency between NP(+) and NP(-) patients.

| Genotype | NP(+) | | | | | | | NP(-) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Kingdom [1] | Cimmino [5] | De Gaudemar [2] | Henriksson [4] | Amaral [12] | Total n | Total % | Kingdom [1] | Cimmino [5] | De Gaudemar [2] | Henriksson [4] | Amaral [12] | Total n | Total % |
| F508del/F508del | 181♦ (57.9%) | 6 (20.6%) | 11 (52.3%) | 17 (41.4%) | 6 | 221 | **51.3** | 3363♦ (49.9%) | 21 (35%) | 23 (51.1%) | 24 (40.6%) | 62 | 3493 | **50** |
| F508del/-severe | 56♦♦ (17.7%) | 7 (24%) | 3 (14.3%) | – | – | 66 | **15.3** | 926♦♦ (13.7%) | 8 (13.3%) | 9 (20%) | – | – | 943 | **13.5** |
| /-mild | _ | _ | _ | _ | 14 | 14 | **3.3** | _ | _ | _ | _ | 23 | 23 | **0.3** |
| /-unknown | 51 | 8 | 3 | 16 | _ | 78 | **18** | 1581 | 12 | 8 | 24 | _ | 1625 | **23.2** |
| subtotal | 107 (34%) | 15 | 6 | 16 | 14 | 158 | **36.6** | 2507 (37%) | 20 | 17 | 24 | 23 | 2591 | **37** |
| unknown/ unknown | 27 | 8 | 4 | 8 | 5 | 52 | **12.1** | 869 | 19 | 5 | 11 | 9 | 913 | **13** |
| 1)+2)+3) | 315 | 29 | 21 | 41 | 25 | **431** | **100** | 6739 | 60 | 45 | 59 | 94 | **6997** | **100** |

'**severe'** mutations: 394delTT, 711+3A>G, C276X, 297-3C>A, W401X, I507del, F508del, 1717-1G>A, G542X G551D, R553X, 621+1G>T, 2183delAA>G, E822X, W846X, 2789+5G>A, 2869insG, Y1092X, R1162X, 3659delC, 3849+10kbC>T,W1282X, N1303K, W1310X, 4218insT,. **'mild'** mutations: R75Q, W79R, P99L, Y109N, R117H, L206W, R334W, R347H, A455E, G628R, S945L, A1067T, N1088D, D1152H, S1235R, G1244V, S1251N, other: unknown mutations, * p = 0.01, ** significant for F508del/G551D only, p = 0.05, %: genotype frequency, n: number of patients in the series, a : data taking into account the only subset of patients in which genotype and the presence or absence of NP were reported.

Table 4. Nasal polyposis (NP) as an unique form of CF: review of the literature.

| Case | Phenotype | | Genotype | | | | | | | | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Mutation nomenclature | | | predictive impact on | | | | |
| | | | | | | | mRNA | protein | | | |
| | age at diagnosis | sweat chloride (mmol/L)* | parental origin | consortium | standardized** | location | | amino acid | domain | structure | |
| 1 | 14 y. | 92-110 | ND | | | | | | | | [25] |
| 2 | 10 y. (twins) | 89-94 | pat. | c.2623G>T | c.2491G>T | ex 14a | decay? | p.E831X | TD2 | absence or truncation by 649 AA [34] | [24] |
| | | | mat. | c.591del18 | c.459del18 | ex 4 | 18 nt deletion | p.I154-159del | TD1 | 6 AA deletion | |
| 3 | 10 y. | 70 | pat. | c.1609C>T | c.1477C>T | ex 10 | decay? | p.Q493X | NBF1 | absence or truncation by 987 AA [27] | this study |
| | | | mat. | c.1342-34 (TG11)(T5) | c.1209-34(T5) | int 8 | exon 9 skipping | pE403_ K464del | NBF1 | misfolded non functional protein [34,36] | |
| | | | | c.1816G>A | c.1684G>A | ex 12 | nt substitution | p.V562I | NBF1 | conductance/ regulation impairment [32] | |
| | | | | c.3149C>A | c.3017C>A | ex 17a | nt substitution | p.A1006E | TD2 | pHi decreased [33] | |

* normal value: < 40 mmol/L,** nucleotide 1=A of the initiator ATG, pat: paternal, mat: maternal, ex: exon, int: intron, AA: aminoacid, ND: not determined.

Table 5. Phenotype associated with CFTR mutation identified in the case report.

| Mutation | Genotype | | | Phenotype | | | | | | | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Homozygosity n | Compound Heterozygosity | | Nasal polyposis/ Sinusitis | Pancreas Insufficiency | Lung disease | | | CBAVD | ↗ Sweat chloride | |
| | | n | 2nd mutation | | | mild | chronic | severe | | | |
| p.Q493X | 2 | | | - | + | + | | | - | + | (27) |
| | | 3 | /F508del | - | + | | | + | - | + | (28) |
| p.V562I | 1 | | | - | + | | | | - | + | (31) |
| | | 1 | /* | - | | | | + | - | + | (29) |
| | | 1 | /T5-(TG)11 | | | | | | + | - | (30) |
| p.A1006E | | 1 | /* | - | | | | + | - | + | (33) |
| IVS8-5T | | 4 | /F508del | **S+NP(1)** | | | | | + | | (38) |
| | | 4 | /W1282X | **S(4)** | | | + | | + | | (38) |
| | | 41 | /** | **S(17)+NP(1)** | | - | - | - | + | + OR - | (39) |
| | | 2 | /** | **NP(1)** | | | +° | | - | - | (40) |
| | | 1 | /W1282X | - | +a | - | - | - | - | - | (41) |

n: number of patients, * second mutation unknown, ** one of the following mutations: F508del, G542X, W1282X, R334W, K1060T, R1066C, R1162X, N1303K, A800G, 2736A>G, 3667ins4. NP: nasal polyposis, S: sinusitis, +: presence of the symptom, -: absence of the symptom reported, a: acute pancreatitis, ° idiopathic bronchiectasis. CBAVD: congenital bilateral absence of vas deferens, empty space: no available data.

21.2% and 25% in NP(+) and NP(-), respectively), due to the limited number of mutations tested among the 1,500 CFTR mutations identified to date. Furthermore, the wide range of panels of mutations tested among the various reports reviewed precluded any comparison of the frequency of a given mutation between NP+ vs. NP- groups, leading us to define subsets of severe, mild, and unknown mutations. By taking these methodological limitations into account, NP was found to be associated with the presence of at least two 'severe' mutations in ≥ 66% of cases 'Table 3', in accordance with a recent study [21] in a CF population, reporting a preferential association of chronic rhinosinusitis and NP with "mild" and "strong" mutations, respectively.

It was therefore interesting to determine whether NP is still associated to 'severe' mutations when it is the only clinical feature of CF. It is difficult to discriminate between NP as a monosymptomatic form of CF or as the initial symptom of typical CF with delayed manifestations. In rare cases, chronic rhinosinusitis or polyposis has been reported as the initial symptom of CF (13/605 patients [22] and 2/893 patients [23]). NP as the unique feature of CF appears to be far more uncommon, as, to our knowledge, only 2 families have been reported to date [24,25]. We report a similar case with no other clinical feature of CF with a follow-up of fifteen years after CF diagnosis. We identified a complex genotype with four CFTR variants, namely, p.Q493X, p.V562I, p.A1006E and IVS8-5T. To our knowledge, such a combination of CF variants has not been previously reported in a CF patient (irrespective of the presence or absence of NP). We then reviewed the clinical features reported in CF patients carrying one of these mutations. p.Q493X is a 'severe' mutation (classical 'CF causing mutation' [26]), first described in 2 homozygous patients with PI, moderate lung disease, and high sweat chloride [27], and subsequently as compound heterozygosity with F508del in 3 PI-CF patients without nasal polyposis [28] (Table 5). The p.V562I variant is of doubtful significance, as it has been considered to be either a non-functional variant [29] or a 'mild' mutation ('CFTR related disorder' [26]) resulting in congenital bilateral absence of vas deferens (CBAVD) in trans association with the IVS8-5T variant [30], or also as a 'severe' mutation, present in the homozygous state in a patient with typical CF disease [31] without NP. A recent functional study suggested that this variant results in alteration of conductance or regulation of the chloride channel [32]. p.A1006E has been detected in the heterozygous state, with no other identified CF mutation, in a patient with mild CF [33] ('wide spectrum' CF mutations without NP). Interestingly, the IVS8-5T variant, responsible for CFTR exon 9 skipping [34-36], irrespective of its association with another CF mutation, is commonly found in patients with sinusitis or NP (Table 5) and mild or absent lung injury [35-44], as in the patient reported herein.

In keeping with our case, two previous case reports have reported NP as the only symptom of CF. A 14-year-old girl [25] and twin brothers [24] were affected with massive recurrent NP

and elevated sweat chloride levels, with no lung or pancreatic injury. CF genotype was determined only in the two brothers, who were found to be compound heterozygotes for two severe CF mutations, namely c.591del18 (exon 4) resulting in a 6 amino-acid deletion in CFTR TD1 domain and p.E831X (exon 14a) truncating CFTR at the TD2 domain level (Table 4). The data of the literature as well as our own data suggest that the presence of nasal polyps is associated with a decreased impact of severe CF mutations on the patient's clinical condition, secondary to genetic/environmental factors that remain to be elucidated.

Whether being a CF carrier ('healthy heterozygote') may predispose to the development of NP is still a subject of debate. A recent study reported 5 (11.4%) F508del carriers in a series of 44 adult patients with isolated NP and a normal sweat test [45]. Two other studies found 7 (11.9%) and 4 (7.3%) carriers in series of 59 and 55 individuals with isolated NP, respectively [46,47], while the carrier frequency is about 3 to 4% in the general population. A limitation of these last two studies was the absence of sweat chloride assessment and CF gene analysis limited to the most common mutations, which therefore precluded formal exclusion of the diagnosis of CF. Interestingly, it has also been suggested that the CF carrier status might predispose to chronic sinusitis without NP; in a series of 147 patients, suffering exclusively from chronic sinusitis and nasal obstruction, 6% were carriers of CFTR mutations, the most common being F508del [48] compared to a prevalence of 3 to 4% in the general population.

It therefore appears useful to test for CF mutations in all patients with 'idiopathic' chronic sinonasal disease, particularly when it is severe and when the usual causes have been excluded. This attitude might have an impact on both patient follow-up and genetic counselling of the patient's relatives.

ACKNOWLEDGMENTS

We gratefully acknowledge the support of the Association 'Mucoviscidose ABCF'

CONFLICT OF INTEREST

No conflict of interest is declared.

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