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Original Article

Sinonasal manifestations of cystic fibrosis: A correlation between genotype and phenotype?☆

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Abstract

Background: Patients with Cystic Fibrosis are prone to develop sinonasal disease. Studies in genotype–phenotype correlations for sinonasal disease are scarce and inconclusive.
Methods: In this observational study several aspects of sinonasal disease were investigated in 104 adult patients with CF. In each patient a disease specific quality of life questionnaire (RSOM-31), nasal endoscopy and a CT scan of the paranasal sinuses were performed. Patients were divided into two groups, class I–III mutations and class IV–V mutations, based on their CFTR mutations.
Results: The prevalence of rhinosinusitis in adult patients with CF was 63% and the prevalence of nasal polyps 25%. Patients with class I–III mutations had significantly smaller frontal sinuses, sphenoid sinuses, more opacification in the sinonasal area and more often osteitis/neoosteogenesis of the maxillary sinus wall compared to patients with class IV and V mutations.
Conclusion: These data suggest more severe sinonasal disease in patients with class I–III mutations compared to patients with class IV–V mutations.

Keywords: Cystic fibrosis; Rhinosinusitis; Nasal polyps; Genotype

1. Introduction

Cystic Fibrosis (CF) predisposes a patient to pathology of the nose and the paranasal sinuses. The mucosa lining the nose and paranasal sinuses is similar to the mucosa of the lower airways. Therefore pathology in both compartments of the respiratory system is expected to be quite identical. In the sinonasal system the CF distinctive viscous mucous results in impaired ciliary function, mucous stasis and consequently bacterial superinfection. Moreover, research showed other factors are associated with the tendency of CF patients to develop sinonasal disease. Evidence suggests that heterozygotes for the Cystic Fibrosis Transmembrane Regulator (CFTR) mutation are predisposed to develop chronic rhinosinusitis compared to the normal wild-type CFTR population (1,2). This might indicate a direct influence of the CFTR mutation in the aetiology of CF sinonasal disease. Another factor that might play a role in the development of sinonasal disease in CF is the environment of the sinuses. Research showed that the immune response in the sinuses is weak, bioavailability of antibiotics is low and the environmental conditions increases antibiotic-resistance of pathogens in the sinuses (3). Altogether this may result in chronic and recalcitrant rhinosinusitis in patients with CF.

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Rhinosinusitis has been proven to negatively influence a patient's quality of life (1,4). Moreover pathogens from the sinuses can migrate to the lungs and cross-infect the lungs (3,5). Often the upper airways barely receive attention in the routine care of the CF patient. Especially in adult patients the upper respiratory tract is not regularly examined. Therefore the actual impact of sinonasal disease in adult patients cannot be estimated properly.

Since the identification of the CF mutation in 1989 approximately 1939 different mutations have been described (6). These mutations can be classified according to their impact on the function of the Cystic Fibrosis Conductance Transmembrane Regulator (CFTR) protein. Class I–III mutations are associated with a severe phenotype of CF. Mutations in class IV–V are associated with a milder CF phenotype (7).

Considerable amount of studies have been performed to find a correlation between the genotype and the phenotype of CF (7,8). Correlations between genotype and phenotype were found for pancreatic function, lung function, age at diagnosis, nutritional status and *Pseudomonas aeruginosa* colonisation (8,9).

Research in a genotype–phenotype correlation for sinonasal disease is scarce and the results are inconclusive. Jorissen and co-workers showed ΔF508 homozygosity was a risk factor for paranasal sinus disease in CF (10). Other investigators showed nasal polyps were more frequent in patients with the genotype consisting of both 'strong' mutations compared to patients with a genotype consisting of unknown or 'mild' mutations (11). However, no association between sinonasal disease and genotype was found in the study of Cimmino et al. (12). Moreover, with their research Sakano et al. displayed no association with the pathology seen on a sinus CT scan and the severity of CF (13). In summary, the current data of a possible genotype–phenotype correlation for sinonasal disease remain inconsistent. Investigating genotype–phenotype correlations can lead to more knowledge on the pathogenesis of sinonasal disease in Cystic Fibrosis. To date this pathophysiology is poorly understood. Besides, a possible correlation can have clinical implications.

In the present prospective study several aspects of sinonasal disease were examined and correlated with genotype in a large group of adult patients with CF.

2. Study design

2.1. Patients

Adult patients who regularly attend the Cystic Fibrosis centre of the Haga Teaching Hospital were studied. All subjects with a diagnosis of CF, based on a positive sweat test and/or genotype were considered eligible for this study. The intention was to include 100 patients. The present study was performed from April 2011 to February 2012 and was approved by the local medical ethics committee.

2.2. Genotype

Patients were divided in two groups; subjects with class I–III mutations and patients with class IV–V mutations. Subjects who were homozygous or compound heterozygous for class I–III mutations were allocated to the class I–III mutation group and patients who carried at least one class IV–V mutation were addressed to the class IV–V mutation group. In patients where one or two CFTR mutations were unknown the sweat test was used to confirm the diagnosis of CF. In those patients pancreatic function and age at diagnosis were used to allocate patients to one of the two groups. Pancreatic function is known to correlate well with genotype (8). Moreover age at diagnosis correlates with genotype as well (9,14). Considering the age at diagnosis a cut-off value of 10 years was used in this study. A subject that was pancreatic sufficient and the age at diagnosis was > 10 years was considered as carrying a class IV–V mutation. Pancreatic insufficiency and age at diagnosis < 10 years was considered among the class I–III mutation group.

2.3. Rhinosinusitis and nasal polyps

In this study rhinosinusitis is defined as an inflammation of the nose and paranasal sinuses characterised by two or more of the following symptoms: nasal blockage/congestion/obstruction, nasal discharge (anterior or posterior), facial pain/pressure and/or a reduction or loss of smell. One of them should be either nasal blockage/congestion/obstruction or nasal discharge. Along with these symptoms either endoscopic signs of nasal polyps, mucopurulent discharge primarily from the middle meatus, oedema/mucosal obstruction primarily in the middle meatus and/or mucosal changes within the ostiomeatal complex and/or sinuses on a CT-scan had to be present (1). In the present study symptoms are measured with the Rhinosinusitis Outcome Measure (RSOM-31). Since this RSOM is a quality of life questionnaire each symptom was scored on a 6-point Likert scale. A symptom was included in the definition of rhinosinusitis when subjects rated the symptom with a 2 ('mild or slight problem') or more.

The presence of nasal polyps was defined as an endoscopically visualised grape-like lesions in at least one nasal cavity following a decongestant (xylometazoline 0.1%).

2.4. Quality of life

Disease specific quality of life (QoL) was measured with the 'Rhinosinusitis Outcome Measure' (RSOM-31)(15). This validated questionnaire consists of 31 items on rhinosinusitis and each item is scored on a 'Magnitude Scale' and an 'Importance Scale'. Since previous experience showed that patients had difficulties in distinguishing between the 'Magnitude Scale' and the 'Importance Scale', in the present study only the 'Magnitude Scale' was measured (J Piccirillo personal communication). The RSOM-31 contains seven domains: nasal, eye, sleep, ear, general, practical and emotional. Disease specific QoL was analysed from the total score on the RSOM-31 divided by the number of completed items, resulting in a 'mean per item' (range 0–5, with higher scores representing a worse quality of life). Since the RSOM-31 contains pulmonary symptoms such as cough and dyspnea, the disease Cystic Fibrosis can influence the outcome of this questionnaire. Therefore the nasal domain of the RSOM-31 was analysed separately.

2.5. Computed tomography

Computed tomography of the paranasal sinuses was performed (Toshiba Aquilion 16). Patients were situated with their head tilted backwards until the palatum durum was positioned perpendicular to the bench. Axial computed tomography was performed with a slice thickness of 0.5 mm and images were reconstructed at 1.0 mm. The scan ranged from the upper border of the frontal sinuses to the lower part of the teeth in the maxilla. No intravenous contrast was used.

Paranasal sinus opacification was assessed using the Lund–Mackay score (L–M score). This validated staging system grades every sinus as 0: normal, 1: partial opacification or 2: total opacification. These points are applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal sinus on each side. The ostiomeatal complex is graded as 0: patent or 1: occluded. The Lund–Mackay score ranges from 0–24. Since CF patients often display aplasia of one or more sinuses the Lund–Mackay score had to be adjusted for this study. The absence of one or more sinuses distort the L–M scores and makes comparison between patients incorrect. Therefore the total L–M score was divided by the amount of developed sinuses or components of the sinonasal system, resulting in a L–M score per component of the sinonasal system. This adjusted L–M score ranged from 0–2. An experienced radiologist (C.J.v.R) analysed all CT-scans and was blinded for genotype and previous study results of the patients.

The volume of the sinuses were analysed with an Aquarius Intuition software (TeraRecon®). For each sinus the circumference on each slice was drawn manually and the total volume of the sinus was calculated subsequently. Volumes of the left and right sides were added up. Only the frontal, sphenoid and maxillary sinuses were measured. Aplastic sinuses were calculated as 0 cm^3.

Moreover increased bone density and irregular thickening, in this study called 'osteitis/neoosteogenesis', of the maxillary sinus wall was evaluated and graded as 0: absent, if both maxillary sinuses did not show osteitis/neoosteogenesis and as 1: present, if one of the maxillary sinuses showed signs of osteitis/neoosteogenesis.

Finally the anatomy of the ostiomeatal complex (OMC) was evaluated. Both left and right OMC were assessed. The anatomy of the OMC was scored as 0: normal on both sides, 1: abnormal anatomy on one or both sides due to sinus surgery in the past or 2: abnormal anatomy on one or both sides without sinus surgery in the past. To ascertain if patients had sinus surgery in the past, surgery reports were requested. In case no surgery reports were available, one experienced otorhinolaryngologist (E.R.), whom was ignorant to previous data of the patients, evaluated the scan and assessed if the patients had surgery on the OMC.

2.6. Data and statistics

Data in this study were analysed with SPSS for Windows, version 17.0. The aspects of sinonasal disease were reported by descriptive characteristics such as mean, standard deviation (SD) and percentage. To determine whether the proportion in the study group takes a particular value (from literature) a z test for a proportion was used. For every aspect of sinonasal disease a comparison between patients with class I–III mutations and patients with class IV–V mutations was made. A chi-squared analysis was applied to rhinosinusitis, nasal polyps and osteitis of the maxillary sinus wall. The RSOM-scores, PSV of the frontal and sphenoid sinuses were analysed using a non-parametric test. The L–M scores and PSV of the maxillary sinuses were analysed using parametric tests. A p-value of <0.05 was considered statistically significant. Since nine hypothesis tests were performed on one population the data had to be corrected for multiple testing. In this study a Holm–Bonferroni correction was applied.

3. Results

3.1. Patients

One hundred and twenty three patients were invited to participate in this study, of which 104 gave informed consent and were included. The mean age of all 104 subjects was 34.8 years (SD: 11.1) and the percentage of male subjects was 52.9%. Fifty-nine patients (56.7%) reported a history with one or more surgeries in the sinonasal area. In total 10 patients were on oral steroids and 41 patients on nasal steroids during the study. The descriptive statistics of the subjects separated for the different mutation classes are displayed in Table 1. This table shows the mean age of patients with class IV–V mutations was significantly higher than the mean age of patients with class I–III mutations (p–value < 0.001). All other descriptive parameters did not differ significantly between the two groups.

3.2. Genotype

In 3 patients one CFTR mutation was unknown and in one patient both of the CFTR mutations were unknown. Table 2 shows the distribution of the genotypes among the 104 study patients. The last column states to which group the patients were assigned. The characteristics of the 3 patients with one unknown mutation are displayed in Table 2. One of the three patients was assigned to the class I–III mutation group and 2 were allocated to the IV–V mutation group. The subject with both unknown mutations was diagnosed at 42 years, but was

Table 1
Descriptive statistics of 104 adult patients with Cystic Fibrosis.

Parameter	Mutation class IV–V	Mutation class I–III	p-Value
	N = 31	N = 73	
Mean age, years (SD)	40.5 (10.7)	32.4 (10.4)	0.000 *
Male, n (%)	14 (45.2)	41 (56.2)	0.304
Previous sinus surgery, n (%)	19 (61.3)	40 (54.8)	0.541
Lung function:			
Mean FEV 1% predicted (SD)	66.3 (25.4)	62.1 (25.5)	0.389
Mean FVC % predicted (SD)	87.5 (18.1)	83.0 (19.0)	0.265
Oral steroids (%)	1 (3.2)	9 (12.3)	0.150
Nasal steroids (%)	9 (29.0)	32 (43.8)	0.158

* p-Value < 0.05.

pancreatic insufficient secondary to a pancreatitis. Since this patient had typical characteristics of 'mild disease' he was assigned to the class IV–V mutation group. In total 73 subjects were allocated to the class I–III mutation group and 31 to the class IV–V mutation group.

3.3. Rhinosinusitis and nasal polyps

Sixty-five patients (62.5%) met the EPOS criteria of the definition of rhinosinusitis. This is significantly higher (p-value < 0.0001) than the 10.9% of chronic rhinosinusitis observed in the general population (16). Table 3 shows the percentage of rhinosinusitis in patients with class I–III mutations was slightly higher than in patients with class IV–V mutations, but the difference was not statistically significant (p-value = 0.14).

In 26 patients (25.0%) nasal endoscopy showed nasal polyps on one or both sides. This observed prevalence is significantly higher (p-value < 0.0001) than the 2.4% observed in the general population (17). Of the 26 CF patients with nasal polyps 21 carried class I–III mutations and 5 class IV–V mutations (p-value = 0.17).

Table 2
Distribution of genotypes and their mutation classes.

Genotype	Frequency; N (%)	Class of mutation
F508del/F508del	61 (58.7)	I–III
F508del/3849 + 10kbC	2 (1.9)	IV–V
F508del/N1303K	2 (1.9)	I–III
F508del/R1162X	2 (1.9)	I–III
F508del/A455E	12 (11.5)	IV–V
F508del/3272-26A > G	5 (4.8)	IV–V
F508del/E528X	1 (1.0)	I–III
F508del/S1251N	3 (2.9)	IV–V
F508del/R75Q	1 (1.0)	IV–V
F508del/G542X	2 (1.9)	I–III
F508del/1717-1G > A	1 (1.0)	I–III
F508del/Ser489X	1 (1.0)	I–III
F508del/4382delA	1 (1.0)	–[a]
F508del/L1077	1 (1.0)	I–III
F508del/1813insC	1 (1.0)	–[b]
A455E/S1251N	1 (1.0)	IV–V
A455E/E60X	1 (1.0)	IV–V
3272-26A > G/G970R	1 (1.0)	IV–V
3272-26A > G/R1162X	1 (1.0)	IV–V
F508del/UNK	2 (1.9)	–[c]
R117H-7T/UNK	1 (1.0)	–[d]
UNK/UNK	1 (1.0)	-[e]
Total	104 (100.4)	

One patient with pancreatic sufficiency and diagnosed at 46 years of age (class IV–V).
[a] Patient with pancreatic sufficiency and diagnosed at 19 years of age (class IV–V).
[b] Patient with pancreatic insufficiency and diagnosed at 9 years of age (class I–III).
[c] One patient with pancreatic insufficiency and diagnosed at 4 years of age (class I–III).
[d] Patient with pancreatic sufficiency and diagnosed at 39 years of age (class IV–V).
[e] Patient with pancreatic insufficiency secondary to chronic pancreatitis and diagnosed at 42 years of age (class IV–V).

Table 3
Aspects of sinonasal disease divided for severity of CF.

Aspect of sinonasal disease	Mutation class IV–V	Mutation class I–III	p-Value
	N = 31	N = 73	
Rhinosinusitis; N (%)	16 (51.6)	49 (67.1)	0.135
Nasal polyps; N (%)	5 (16.1)	21 (28.8)	0.173
RSOM-31 total score; mean (SD)	1.21 (0.77)	1.15 (0.66)	0.672
RSOM-31 nasal domain; mean (SD)	1.44 (0.97)	1.51 (0.85)	0.536
L–M score per component[a]; mean (SD)	0.62 (0.41)	0.85 (0.32)	0.007 *
PSV frontal sinuses[b] (cm^3); mean (SD)	5.09 (5.00)	2.34 (2.96)	0.002 *
PSV sphenoid sinuses[b] (cm^3); mean (SD)	3.79 (4.58)	1.74 (2.18)	0.000 *
PSV maxillary sinuses[b] (cm^3); mean (SD)	18.83 (8.42)	17.17 (7.70)	0.331
Osteitis maxillary sinuses; N (%)	21 (67.7)	67 (91.8)	0.002 *

[a] Lund–Mackay score per component of sinonasal system.
[b] PSV = Paranasal sinus volume.
* Statistically significant after Holm–Bonferroni correction.

3.4. Quality of life (RSOM-31)

The mean total score on the RSOM-31 of the total study population was 1.17 (SD: 0.70). The mean score on the nasal domain was 1.49 (SD: 0.88). Table 3 displays the RSOM scores for the two groups based on mutation classes. Statistical analyses showed no significant difference between these two groups for the total score and the nasal domain (p-value = 0.67, respectively p-value = 0.54).

3.5. Computed tomography

Of the study population 15 patients showed aplasia of both frontal sinuses (20.0% class IV–V, 80.0% class I–III). Eight patients had one aplastic frontal sinus (12.5% class IV–V, 87.5% class I–III). Moreover two patients displayed aplasia of one sphenoid sinus (both with class I–III mutations). In one patient very extensive sinus surgery leads to indistinct boundaries of the sinuses and therefore this patient was not included in the analysis of the L–M scores. This patient was carrying two class I–III mutations.

The mean L–M score per component of the sinonasal system for 103 patients was 0.78 (SD: 0.37). Table 3 shows the L–M scores in patients with class I–III mutations were significantly higher compared to patients with class IV–V mutations (p-value = 0.007).

Paranasal sinus volume was analysed in all 104 patients. The mean volume of the left and right frontal sinuses together was 3.16 cm^3 (SD: 3.87). For the sphenoid sinuses the mean volume was 2.35 cm^3 (SD: 3.21). The mean volume of both maxillary sinuses together was 17.66 cm^3 (SD: 7.92). Table 3 presents the volumes of these sinuses for patients with class IV–V mutations and class I–III mutations. The frontal sinuses and the sphenoid sinuses of patients with class I–III mutations were significantly smaller compared to patients with class IV–V mutations (p-value = 0.002, respectively p-value = 0.000).

Among the study population 88 patients (84.6%) had signs of osteitis/neoosteogenesis in one or two maxillary sinuses. This percentage was significantly higher in the group of patients with

class I–III mutations compared to patients with class IV–V mutations (p-value = 0.002, Table 2).

Analysis of the ostiomeateal complex showed a normal anatomy on both sides in 43 patients (41.3%), an abnormal anatomy on one or both sides with sinus surgery in the past in 45 patients (43.3%). In 16 patients (15.4%) the CT-sinus showed an abnormal anatomy of the ostiomeatal complex without any reported sinus surgery in the past or without signs of previous sinus surgery on the CT-scan. This abnormal anatomy often involved the uncinate process, where this process was projected medially instead of laterally (Fig. 1a and b).

4. Discussion

The sinonasal system is gradually receiving more attention in the treatment of the multi-organ disease Cystic Fibrosis. Pathology of the nose and the paranasal sinuses in CF patients have been observed previously. Only recently more substantial research in this area was initiated. Where previous studies include a rather heterogeneous study population with children and adults with CF, the present study focuses on a large group of only adult patients.

Table 1 showed the characteristics of the two groups were almost comparable. However, the mean age differed significantly, with a higher mean age in the patients with class IV–V mutations. One could speculate this is the result of the fact that class IV–V mutations often leads to a higher life expectancy. For this reason the group of patients with class IV–V mutations contained relatively older patients compared to the group of patients carrying class I–III mutations.

Since CF predisposes a patient to rhinosinusitis, the high prevalence of this complication was expected. In total 65 patients fulfilled the criteria of the EPOS for rhinosinusitis. This prevalence among CF patients is considerably higher compared to the prevalence in the general population. However, the prevalence in the general population from the GA2LEN study was the prevalence of chronic rhinosinusitis. One limitation of this study is that the time aspect of the rhinosinusitis in the study population is unknown. Where in the GA2LEN study was asked for symptoms >12 weeks in the previous 12 months, we only asked for symptoms in the last 2 weeks. Therefore one might suggest that these two prevalences cannot be compared to each other, although considering the CT-scans of these patients, a chronic course of this rhinosinusitis is suspected. The investigators feel the high prevalence of rhinosinusitis and nasal polyps among adult patients with CF should indicate a closer follow-up of this pathology by the pulmonary physician as well as the otorhinolaryngologist.

In the present study we chose to use a 'mean per item' outcome of the RSOM-31 to ensure we could include the incomplete questionnaires in the analyses. However, this method is not previously used in other studies. To compare data of CF patients with data of patients suffering from chronic rhinosinusitis (CRS), we could calculate 'mean per item' scores in other studies. For the study of Dietz de Loos and colleagues (18) this calculated mean total RSOM score in patients with CRS and nasal polyps was 2.13 and for patients with CRS without nasal polyps this was 2.16.

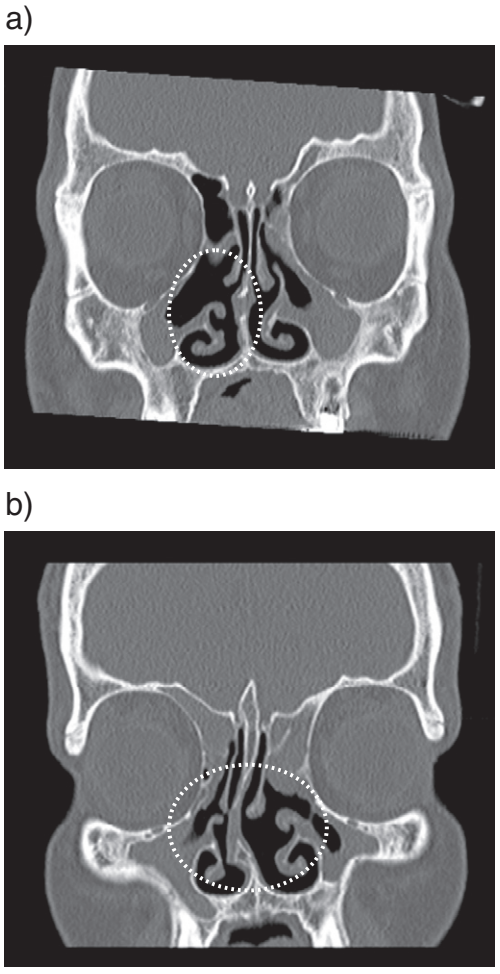

Fig. 1. a) Abnormal anatomy of uncinate process on right side, normal anatomy on left side. b) Bilateral abnormal anatomy of uncinate process.

Compared to our results of 1.21 and 1.15 for the class IV–V mutation group and the class I–III mutation group, respectively, the reported symptoms of CF patients were lower. Results of Hissaria et al. confirm this observation with a mean total RSOM score of 2.2 in patients with sinonasal polyposis (19). This could suggest that CF patients tend to underestimate the rhinosinusitis symptoms. One could speculate this is explained by a more chronic or perhaps congenital course of rhinosinusitis in CF patients or this could be due to other pathology, for example pulmonary and gastrointestinal disease, that outweigh sinonasal disease.

In this study we used a modified Lund–Mackay score. Since many CF patients display aplasia of the frontal sinuses, the original L–M scoring system cannot be used accurately in these patients. Therefore the investigators chose to use an adjusted L–M score, the L–M score per component of the sinonasal system. For this reason comparison with literature required adaptation of the data. Dietz de Loos et al. showed a mean L–M score of 18 in 137 patients with CRS and nasal polyps and a mean score of 5 in 97 patients with CRS but no nasal polyps (18). Corrected for the 4% of the general population with two aplastic frontal sinuses (20), the L–M score per component of the sinonasal system would be 1.51 for patients with CRS and nasal polyps and for patients with CRS without nasal polyps

this would be 0.41. Our CF population had a mean L–M score intermediate of those two CRS subpopulations of 0.78.

In our study patients with class I–III mutations had significantly smaller frontal and sphenoid sinuses compared to patients with class IV–V mutations. For the maxillary sinuses this difference did not reach statistical significance. These findings were supported by several studies (20–23). To date the exact pathogenesis of abnormal paranasal sinus development is unknown. A commonly held hypothesis is that chronic sinusitis during development decreases sinus pneumatization, leading to smaller sinuses (20). Considering this hypothesis, one could speculate patients with class I–III mutations develop chronic sinusitis earlier in life compared to patients carrying class IV–V mutations. Consequently, pneumatization is reduced or not even initiated, resulting in hypoplastic or aplastic sinuses respectively. The fact that the maxillary sinus is relatively well developed and no difference between the two study groups was detected, could be explained by the timing of pneumatization. The maxillary sinuses pneumatize prenatally, while the frontal and sphenoid sinuses develop after birth. Since sinusitis can only develop postnatal, it can interfere with the pneumatization of the frontal and sphenoid sinuses more compared to pneumatization of the maxillary sinus. Interestingly, Chang et al. contradict the previous hypothesis and state that sinus hypoplasia precedes sinus infection in a porcine model of CF. They suggest a direct influence of the CFTR protein on sinus development (24). The residual CFTR function in patients with class IV–V mutations as opposed to no CFTR function in the class I–III mutation group could explain our observation of smaller sinuses in severe CF. The volume of the ethmoid sinus was not analysed in this study, since this was technically difficult. Where the other sinuses had distinct boundaries to draw a circumference, the ethmoid sinus has less distinct boundaries. For this reason only opacification of the ethmoid sinuses was evaluated. Like the maxillary sinus the ethmoid sinus pneumatizes prenatally. None of the patients showed aplastic ethmoid sinuses, however the investigators did see signs of hypoplasia, in example fewer ethmoid cells. This observation was in concordance with data from Eggesbo and colleagues (20).

Osteitis/neoosteogenesis in patients with rhinosinusitis is associated with increased severity of inflammation (25). The extent of osteitis has been correlated with the Lund–Mackay score, duration of symptoms and previous surgery (26). Our findings that patients with class I–III mutations showed significantly more often osteitis of the maxillary sinus compared to patients with class IV–V mutations, could indicate the patients with class I–III mutations experience increased severity of inflammation in the paranasal sinuses compared to the class IV–V mutation group.

Although the exact pathogenesis of sinonasal disease is not entirely clarified, one could speculate on a rationale for the sinonasal phenotype to be affected by CFTR genotype. One explanation could be that class I–III mutations result in higher viscosity of the sinonasal mucus and therefore rhinosinusitis is more easily developed compared to class IV–V mutations. Furthermore, the sinonasal system could be directly related to the function of the CFTR protein at the apical membrane of the sinonasal mucosa. Wang and co-workers (2) showed that carriers of a CFTR mutation are predisposed to develop chronic rhinosinusitis compared to the normal wild-type CFTR population. Previous research showed that heterozygote carriers of CFTR mutations have approximately 50% of the normal CFTR function compared to wild-type CFTR, which is sufficient to remain free of disease (27). Patients with class IV–V mutations have a decreased CFTR function, but they often have residual CFTR function. This residual function could result in sinonasal disease, but not as severe as in patients with no CFTR function, such as patients with class I–III mutations. Thus, CFTR function could be directly related to the development of rhinosinusitis.

To our knowledge, this is the first study to describe the specific abnormal anatomy of the uncinate process in patients with CF. Previously, medial bulging of the lateral nasal wall, aplasia/hypoplasia of the uncinate process and demineralization of the process have been observed in CF patients (23,28–31). According to the investigators this bulging and demineralization were associated with a maxillary sinus mucocele. Absence or hypoplasia of the uncinate process may follow maxillary sinus hypoplasia (32). However, in our study population we did not find any signs for a maxillary mucocele. Moreover the anatomy we observed did not resemble hypoplasia. The uncinate process was projected medially towards the nasal septum, instead of projected in an upwards direction. Remarkably this anatomy results in a wide and open infundibulum, which in theory facilitates good drainage from the sinus to the nasal cavity.

To date, the pathogenesis of sinonasal disease in CF is not fully elucidated. Research in children with CF is needed to investigate the beginning of sinonasal disease in CF. The results of the present study emphasise that rhinosinusitis in CF patients is chronic, but unfortunately the onset of this extensive pathology is unknown.

In summary this observational study showed the prevalence of rhinosinusitis in adult patients with CF was 63% and the prevalence of nasal polyps was 25%. Patients with class I–III mutations had significantly smaller frontal sinuses, sphenoid sinuses, more opacification in the sinonasal area and more often osteitis/neoosteogenesis of the maxillary sinus wall compared to patients with class IV–V mutations. Despite this considerable sinonasal pathology, patients do not estimate these problems as very troublesome. For this reason the investigators recommend a regular examination of the sinonasal area in all CF-patients.

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