Retrospective Analysis of Chronic Rhinosinusitis in Patients With Cystic Fibrosis

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Abstract
Introduction: Chronic rhinosinusitis (CRS) is very common in patients with cystic fibrosis (CF). This can be explained by the unified airway concept, where the same pathophysiological phenomenon that affects the lungs, affects the paranasal sinuses (PNS). The management of these cases is difficult.

Objective: To describe the teamwork of otolaryngologists and bronchopulmonary specialists in patients with CF.

Method: We performed a descriptive, retrospective study over the last 17 years, which included 14 patients with CRS and CF attended at a private hospital.

Results: Of the patients, 64% were male and the median age was 23 years. The most frequent mutations found were ΔF508, M470 and R553. All of the patients with ΔF508 mutation had nasal polyps. 100% of the patients had clinical findings of CRS. All the patients had had endoscopic nasal surgery. The median number of endoscopic surgeries was 2.

Conclusions: Given the high prevalence of CRS in patients with CF, everyone should have a computed tomography scan of the PNS during the initial assessment, considering that sinus germs are the ones that colonise the lower airway. The otolaryngologist should be part of the CF team. Before receiving a lung transplant or in cases of chronic headache, endoscopic surgery should be performed in patients in whom medical treatment fails to clear the sinuses because this infection is the one that colonises the lower airway.

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PALABRAS CLAVE
Rinosinusitis crónica; Fibrosis quística; Cirugía endoscópica nasal; Otorrinolaringólogo

Análisis retrospectivo de pacientes portadores de rinosinusitis crónica por fibrosis quística

Resumen
Introducción: La rinosinusitis crónica es muy frecuente en pacientes con fibrosis quística, lo que se puede explicar por el concepto de vía aérea unificada, donde el mismo fenómeno


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Introduction

CF is an autosomal recessive, progressive genetic disorder which has an incidence of 1 case per 3000 individuals of white race. It is caused by mutations in a gene encoding the regulatory protein for CF transmembrane conductance regulation (CFTR), resulting in deregulation in the transport of chloride and sodium in the apical surface of cells, causing thick viscous secretions in the lungs, pancreas, intestine, and reproductive system.

It is important to note that the concept of a unified airway is of great relevance in CF. The same underlying pathophysiological process which affects the lungs also affects the PNS, where there is a thickening of mucus resulting in impaired mucociliary movement and bacterial colonisation, leading to secondary chronic sinus inflammation, with globular cell hyperplasia, squamous metaplasia, and loss of ciliated cells. At a macroscopic level, these factors obstruct sinus drainage leading to mucus stasis and resulting in local infection and inflammation which mostly affects the ostia. Secretions become trapped in the PNS, reducing gaseous exchange between the sinuses and the bloodstream and leading to increased CO₂ partial pressure. This, in turn, results in mucosal oedema, decreased ciliary function, and bacterial colonisation. These changes translate into clinical symptoms, mainly in the form of sinonasal polyps and nasal obstruction. Thus, CRS is very common in patients with CF. There have been reports of involvement of the PNS in the paediatric population in over 90% of cases, with a high incidence of nasal polyps, ranging between 6% and 48% of patients, developing around the age of 5 years according to various studies. These polyps are different from those appearing in atopic patients: they have a thin basal membrane, with no hyalinisation of the mucosa, fewer eosinophils and predominance of neutrophils and abundant acid mucin in the mucous glands. Recent publications have reported a high correlation between the germs cultured in the PNS and in bronchoalveolar lavage (BAL), thus indicating that the upper airway is often colonised by the same microorganisms as the lower airway, which subsequently damage the lung in a chronic manner, largely determining the fatal prognosis of this disease. The bacteria most frequently isolated in the PNS of CF patients are Pseudomonas aeruginosa and Staphylococcus aureus, which are found in macrocolonies forming biofilms, providing them with a barrier against antimicrobial agents and inflammatory cells and promoting bacterial resistance.

CRS is difficult to manage in general, but especially when due to CF. Once diagnosed, treatment should be based on treating the infection and maintaining patent PNS through medical treatment and/or endoscopic sinus surgery (ESS). This enables good drainage of secretions from the PNS, reducing lower airway infections secondary to their accumulation and, thus, progression of the disease. Therefore, otorhinolaryngologists (ENT) play a vital role in the management of these patients and must work as a team with bronchopulmonary specialists in CF. However, the percentage of ENT consultations for this reason is not very high. The reason for this is thought to be that radiological findings do not always appear in conjunction with sinonasal symptoms. Furthermore, it may also be that the severity of pulmonary symptoms often makes patients prioritise attention to other clinical manifestations of the disease, thus underestimating or adapting to the sinonasal problems and not consulting for them.

The present study describes the teamwork between ENT and bronchopulmonary specialists for 17 years in 14 patients with CF.

Methods

We conducted an observational, descriptive, retrospective study of patients with CRS due to CF, who were treated in the previous 17 years at a private clinic. For this study, we selected patients with confirmed diagnosis of CF by sweat test or genetic test, diagnosed with CRS according to the
criteria of the American Academy of Otolaryngology and Head and Neck Surgery. This study was approved by the ethics committee of the clinic.

**Data Collection**

We identified patients treated at the centre according to the criteria described previously and reviewed their medical records. The studied variables were: age, gender, age at diagnosis of CF, result of the sweat test and genetic testing if available, type of CRS (polypoid or non-polypoid), CT classification of PNS, age at the first ESS, number of surgical reinterventions, PNS and BAL cultures and history of lung transplantation.

Confirmed cases of CF were defined by a sweat test with quantitative pilocarpine from a laboratory confirming a chloride result over 60 mEq/l. Normal sweat tests were considered for chloride values up to 40 mEq/l and indefinite (or borderline) as 40–60 mEq/l (Gibson and Cooke technique). Diagnostic confirmation of cases by positive genetic test for CF were obtained from an independent clinical laboratory by polymerase chain reaction (PCR), study of gel electrophoresis and sequencing of the 27 exons of the CFTR gene, including 20 bp towards the 5’ and 3’ ends of each intron, which can identify 1300 alterations in the CFTR gene.

Following the criteria of the American Association of Otolaryngology, we defined the presence of CRS as 2 or more of the following signs and symptoms: mucopurulent discharge (anterior, posterior or both), nasal obstruction, pain, facial pressure or fullness, decreased olfaction for over 12 weeks and inflammation documented by one or more of the following findings: purulent mucus or oedema in the middle meatus or ethmoid region, polyps in the nasal cavity or middle meatus and/or radiological imaging tests showing inflammation of the PNS. We evaluated the presence of nasal polyposis through an endoscopic test performed by an otolaryngologist.

We used the CT classification of PNS by Lund–Mackay to evaluate the radiological characteristics of PNS. We assigned a score from 0 to 2 (0=no abnormalities, 1=partial opacification, 2=total opacification) to each of the PNS (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal) on each side (right, left). Additionally, we assessed the ostiomeatal complex (0=unobstructed, 2=obstructed). Thus, the total score ranged from 0 to 24.

The surgical procedure performed on these patients was ESS expanded for CF, and carried out by the same otolaryngologist. The technique consisted in extending the ostium of the maxillary sinus to the bottom of the nostril, excising the corresponding portion of the inferior turbinate, along with ethmoidectomy, sphenoidectomy and opening of the frontal sinus, as appropriate in each case. Surgical reoperations were mainly for review and cleaning of the PNS with BAL for recurrence of infectious and polypoid diseases, in conjunction with pulmonary decompensation due to infection of the upper and lower airways.

**Statistical Analysis**

We conducted descriptive statistics for sociodemographic variables. The results are presented as percentages for nominal variables and as means and interquartile ranges for quantitative variables with nonparametric distribution. We used quartile remission with the mean Lund–Mackay score to evaluate the relationship with the presence of polyps according to the CT classification of PNS.

**Results**

A total of 14 patients with CF and CRS participated in the study, of which 64% were male. The mean age was 23 years (interquartile range [IR]: 19–27 years), ranging between 15 and 52 years.

The mean age at diagnosis of CF was 43.5 months (IR: 6–130 months). The lowest value was at 2 months and the highest value was at 18 years and 2 months. The sweat test was normal in 5/14 patients (35.7%), in the intermediate range in 1/14 patients (7.1%) and abnormal in 8/14 patients (57.1%). The mean chloride result in the sweat test was 83.05 mEq/l (IR: 23.1–101.9 mEq/l).

We studied the type of genetic mutation in 9/14 patients (64%), as described in Table 1. The most frequent mutations found in this group were ∆F508 in 5 patients and M470 and R553 in 2 patients, respectively. All the patients (100%) with the ∆F508 mutation presented polyps.

All of the patients (100%) suffered CRS symptoms as defined by the American Academy of Otolaryngology. Of these, 10/14 (71.4%) patients presented polypoid CRS and 4/14 (28.6%) patients presented non-polypoid CRS. Out of the patients with polyoid CRS, 50% presented the ∆F508 mutation. According to the CT classification by Lund–Mackay, patients with CF presented a mean score of 24 points, corresponding to the maximum score (IR: 18–24 points, with a minimum of 7 points in 1 patient). There was no significant variation in the Lund–Mackay score among patients with CRS with and without polyps (P=1).

In total, 3/14 (21.4%) patients underwent lung transplantation, 2 of them at 13 years of age and the third at age 23.

All CF patients with CRS underwent ESS. The youngest did so at 4 years of age and the eldest at 48 years of age. The mean age at which the first ESS took place was 14.5 years (IR: 13–19 years). Cultures of the PNS with BAL were taken during surgery. The most frequently isolated microorganisms were *P. aeruginosa*, *S. aureus* and *Streptococcus viridans*. The mean number of reoperations was 2 ESS (IR: 0–3).

The 3 patients who underwent lung transplantation presented altered sweat test results, with only 1 of them having a genetic study available. All underwent ESS before lung transplantation and presented CRS with polyps and maximum Lund–Mackay score (24 points). One of them was reoperated on 4 occasions after the transplant. The details of the diagnosis of CF and ESS in these patients are described in Table 2.

**Discussion**

The diagnosis of CF in our study group was performed by a sweat test in 8/14 patients. In those with a normal or intermediate sweat test result and in 3 patients with altered sweat test, the study was complemented by genetic testing for CF. This indicated that symptoms were prevalent
in the diagnosis of CF. Therefore, it is very important to obtain a genetic study which clarifies diagnostic doubt for cases of normal sweat tests in which clinical suspicion of CF still remains. This is especially true for the Chilean population, since there is no genetic pool describing the mutational characteristics of CF within the population.

As described in the literature and observed in the cases presented in this study, almost 100% of CF patients suffered CRS.² It has been observed that there is a higher incidence of CF gene mutations in the population with CRS than in the general population.¹¹,²²,²³ The presence of polyps is also related to the type of CF mutation. These are more common in patients with 2 "strong" mutations,²⁴ especially the classic ΔF508 mutation and the G551D mutation.²⁴,²⁵ In our study, 100% of patients with the classic mutation presented CRS with polyps.

Regarding the diagnosis of CRS, the presence of symptoms is rare, so it is necessary to supplement the assessment with more objective tests.⁵,¹⁹,²⁶,²⁷ A study of 34 patients with CF found 20.6% of CRS according to a questionnaire, 73.5% of CRS observed by nasofibroscopy and 93.5% of CRS revealed by a CT scan of the PNS. The variation found between the images and the symptoms may be due to lesser attention being paid by these patients to sinonasal symptoms and signs compared with other, more severe, clinical manifestations of the disease. In addition, there could be an adaptation to the symptoms which decreased their discomfort and a lack of knowledge of sinonasal disease and how it can influence the quality of life and pulmonary disease progression.⁴,²⁰ According to Boari, endoscopy appears to be the most sensitive method for detecting CRS, since it identifies sinonasal abnormalities despite there being no clinical suspicion of CRS. Therefore, it should be performed periodically among these patients.⁵ For the same reason, the contribution of otorhinolaryngologists in the monitoring of CF is notable.

Medical management should be the first line treatment for CRS due to CF, in an attempt to restore ventilation and drainage of the sinonasal tract and improve mucociliary clearance. Ideally, cultures of the middle meatus should be taken in order to treat infections. In addition, nasal irrigation with hypertonic solutions should be performed in order to remove debris and crusts,²⁸-³¹ and topical medication should also be applied. Unfortunately, there comes a point when inhalation therapies cease to work, so an effective treatment of sinonasal disease depends significantly on surgery.²,⁷,⁹,³² Nevertheless, ESS is not a definitive treatment for CRS and the tendency is towards relapse, with a higher frequency than in other cases of CRS.²,⁹,₂⁶,₃₃,₃₄ The aim of ESS is to extend the drainage osium of the cavities so as to facilitate, on the one hand, a better drainage of thick secretions and, on the other hand, the entry of saline washings which patients should perform methodically. Moreover, it also aims to facilitate the taking of culture samples from the PNS operated during exacerbation periods of CRS and the access of local treatments with nebulised antibiotics.

Indications for ESS in CRS due to CF correspond to: prolonged RS unresponsive to medical treatment of at least 6 months evolution, persistent headache,³⁴ pulmonary exacerbation associated with RS, mucocele and before lung transplantation.³⁵ Ideally, the use of a tamponade during surgery is not recommended; however, if its use becomes necessary, then this should be left for the shortest time possible and preferably removed within 24 h. Isolated polypectomy without ESS should not be done, as it is less effective.² Some studies have shown that ESS has significant benefits on CRS symptom scores and endoscopic scores.⁴,³⁴,³⁶ Orbitofrontal headache requires special attention, since it is the symptom with less improvement after surgery and may indicate recurrence of frontal mucopyocele and the presence of intracranial complications of CRS.³⁴

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation</th>
<th>CRS With Polyps</th>
<th>Lund–Mackay Score</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>ΔF508/M470</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>ΔF508/R553 X</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>ΔF508/R553 X</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>ΔF508/F50</td>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>ΔF508/p.N1303 K</td>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>542X/1078 del</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>R334 W/T3515/M</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>997F/F834/7 T/9 T</td>
<td>No</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>M470V/M470</td>
<td>No</td>
<td>24</td>
</tr>
</tbody>
</table>

**CF:** cystic fibrosis; **CRS:** chronic rhinosinusitis.

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis of CF, Months</th>
<th>Sweat Test (Chlorine), mEq/l</th>
<th>Genetic Mutation</th>
<th>Age at Transplant, Years</th>
<th>Age at First ESS, Years</th>
<th>Reintervention, ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>72.5</td>
<td>None</td>
<td>16</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>101.9</td>
<td>ΔF508/p.N1303 K</td>
<td>13</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>103.8</td>
<td>None</td>
<td>13</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

**CF:** cystic fibrosis; **CRS:** chronic rhinosinusitis; **ESS:** endoscopic sinus surgery.
Given the high recurrence of CRS with or without polyps in this disease, it is only reoperated when there is an imbalance of the lower airway or when the degree of nasal obstruction prevents adequate ventilation. However, these patients often require reintervention, so it is very important to preserve the anatomical repair points, such as the middle turbinate, which guide subsequent surgeries. According to different studies, the mean time interval between surgeries is variable and ranges from 18 to 48 months.26,33

It has been reported that treatment of CRS is essential to reduce its negative impact on transplanted lungs for patients with CRS due to CF with lung transplants. It has been observed that a decrease in colonisation of the upper airway diminishes colonisation of the lower airway, the rate of pneumonia and tracheobronchitis and the incidence of oblitative bronchiolitis.16,37 If lung conditions permit it, ESS should be performed prior to transplantation.5 If the patient’s condition is very deteriorated, ESS will be performed after recovery from the transplantation.

Saline nasal irrigation is recommended to minimise symptoms and exacerbations of CRS and subsequent to ESS.29,30,38,39 This should be done with syringes in order to obtain a good washing of secretions,5 since nebulisers are not capable of displacing them and saline sprays only penetrate in up 3% of operated PNS.40 The benefits of nasal irrigation include improvement in mucociliary clearance, decreased oedema of the nasal mucosal and mechanical movement of debris and allergens, which in turn improve nasal function and reduce symptoms. However, the exact mechanism of action of saline washes is not clearly known.41,42 Hypertonic saline washes have shown greater benefits than isotonic ones and especially improve mucociliary clearance.43-46 Tobramycin can also be used during postoperative management in daily nasal irrigations.3 Although the use of mometasone is not supported by the medical literature, in the empirical experience of the senior author, using it as an adjuvant therapy helps to reduce inflammation of the PNS and nasal passages and aids in controlling the recurrence of polyps and infection, especially in cases of CRS with polyps. After hospital discharge, ENT controls must be followed in order to obtain serial cultures: monthly during the first 6–9 postoperative months and then according to the evolution, always maintaining regular monitoring by the otorhinolaryngologist. A count greater than or equal to 10⁷ colonies in PNS aspirate should be considered positive. An adequate control of infection reduces recurrences, but success depends primarily on patient adherence to daily nasal washes and regular controls.

Conclusions

A sweat test remains the test of choice for the initial diagnosis of CF in our environment due to the impossibility of carrying out genetic testing on all our patients. However, genetic testing is still indispensable in cases where the sweat test is negative or inconclusive and the symptoms are suggestive of the disease. The ideal situation would be to conduct a genetic study of all patients.

Given the high prevalence of CRS among patients with CF, all of them should undergo a CT scan of PNS during their initial assessment. This becomes even more important when we consider that germs from the PNS are precisely the ones which colonise the lower airway. Thus, otolaryngologists must be an integral part of CF teams.

ESS should be performed in those patients in whom medical treatment fails to clear the PNS and infection colonises the lower airway. In addition, it is also indicated for patients who are to undergo lung transplantation or in cases of chronic headache.

ESS does not follow the basic principles which apply to this surgery in classical CRS, as this must be an ESS procedure extended with large ostia which facilitate drainage of the PNS, given the lack of mucus drainage existing in CF. This type of surgery enables better nasal washings for patients and also facilitates obtaining of PNS bacterial cultures by otolaryngologists during the postoperative period in cases of CRS exacerbation.

Recurrence of sinonasal disease is very common and patients often need to be reoperated more than once. Thus, it is very important to maintain anatomical repair points, such as the middle turbinate, during the ESS intervention.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References