The Connection between Cystic Fibrosis and Chronic Rhinosinusitis: A Comprehensive Review

Amin Javer* and Leilynaz Malekafzali
Department of Surgery, University of British Columbia, Canada

Abstract

**Objective:** The purpose of this paper is to provide an overview on chronic rhinosinusitis (CRS) and cystic fibrosis (CF) and propose a future study to identify the prevalence of CF in patients with recalcitrant CRS.

**Sources of information:** PubMed was searched for articles using the terms Cystic fibrosis, Chronic rhinosinusitis, CRS, and CF. Other relevant guidelines, presentations and resources were used.

**Main Message:** CRS is an inflammatory condition involving nasal and sinus mucosa that lasts for 12 weeks or longer. Difficult-to-treat or recalcitrant CRS is defined as patients who have persistent symptoms despite receiving appropriate medical and surgical therapy. There are various factors that should be considered in patients with recalcitrant CRS that may contribute to the persistence or recurrence of CRS such as CF. CF is an inherited disorder that develops as a result of mutations in the gene coding for the cystic fibrosis transmembrane regulator (CFTR). CRS has been reported in 30% to 67% of patients with CF over all age groups. Additionally, higher rate of CFTR mutations have been reported in patients diagnosed with CRS.

**Conclusion:** Limited research has been conducted to determine the prevalence of undiagnosed CF in adult patients with recalcitrant CRS. We suggest an observational study, where adults with recalcitrant CRS are recruited, and sweat chloride testing and CF genetic analysis by blood tests are done on the patients to find the prevalence of CF in patients with recalcitrant CRS. This area of research needs attention, since patients who suffer from recalcitrant CRS with identifiable CFTR dysfunction may benefit from CF-targeted therapies. Therefore, the diagnosis of CF in patients with recalcitrant CRS would benefit the patients by optimizing their treatment management.

**ABBREVIATIONS**

- CRS: Chronic Rhinosinusitis
- CF: Cystic Fibrosis
- CFTR: Cystic Fibrosis Transmembrane Regulator

**INTRODUCTION**

Chronic rhinosinusitis (CRS) is an inflammatory condition involving nasal and sinus mucosa that lasts for 12 weeks or longer [1,2]. Patients who have difficult-to-treat or recalcitrant CRS have persistent symptoms despite receiving appropriate medical and surgical therapy [3].

Cystic fibrosis is an inherited disorder caused as a result of mutations in the gene coding for the cystic fibrosis transmembrane regulator (CFTR) [4]. CFTR mutation causes dysregulation of water and electrolytes in CF patients, and affects organs such as lung, liver, gut, pancreas and sweat glands [5]. The pulmonary manifestations have been identified as the main cause of morbidity and mortality in CF patients [5].

CRS has been reported in 30% to 67% of patients with CF over all age groups [2]. Additionally, previous studies have identified higher rate of CFTR mutations in patients diagnosed with CRS. Limited research has been conducted to determine the prevalence of undiagnosed cystic fibrosis (CF) in adult patients with recalcitrant chronic rhinosinusitis (CRS). This area of research needs attention, since patients who suffer from recalcitrant CRS with identifiable CFTR dysfunction may benefit from CF-targeted therapies. The purpose of this paper is to provide an overview on CRS and CF and propose a future study to identify the prevalence of CF in patients with recalcitrant CRS.

**Chronic Rhinosinusitis (CRS)**

Rhinosinusitis is an inflammatory condition involving the nasal (rhinitis) and sinus mucosa (sinusitis) [1]. Rhinitis and sinusitis are often co-existing conditions, and specialists have reached a consensus that acute and chronic sinusitis is often associated with rhinitis [1]. This is further supported by the presence of similar expression of inflammatory mediators in ethmoidal and nasal mucosa of patients with rhinosinusitis [1]. However, rhinitis might be present without sinusitis in conditions such as allergic rhinitis [1].
Based on the duration, rhinosinusitis can be classified as acute if it is less than 4 weeks in duration, and chronic if it lasts more than 12 weeks [2]. Acute rhinosinusitis can be further distinguished into viral and bacterial rhinosinusitis [2].

Chronic rhinosinusitis (CRS) is characterized by the presence of at least two of the four cardinal clinical symptoms (nasal drainage, nasal obstruction, hyposmia/anosmia, facial pain/pressure) for at least 12 weeks in addition to objective evidence on physical examination or radiology [2]. In terms of the prevalence of the symptoms, nasal obstruction is the most common (81% to 95%), followed by facial pressure (70% to 85%), discolored nasal discharge (51% to 83%) and decreased sense of smell (61% to 69%) [2]. Although the presences of two or more symptoms for more than 12 weeks are very sensitive for diagnosis of CRS, it is not specific [2]. Therefore, objective evidence through physical examination or radiography is needed for establishing the diagnosis [2]. Physical examination can include the inspection of the nasal cavity using anterior rhinoscopy and nasal endoscopy to assess mucopurulent drainage, edema, and polyps [6]. Further, imaging studies such as non-contrast CT can be used to evaluate the paranasal sinuses [6].

CRS can be classified into three subsets: CRS with nasal polyps (CRSwNP), CRS without NP (CRS sino NP, CRSsNP), and classic allergic fungal rhinosinusitis (AFRS) [7]. The presence of bilateral nasal polyps in the middle meatus is required for the diagnosis of CRS with NP [7].

The pathophysiology of CRS is poorly understood and is believed to be a multifactorial inflammatory process involving the host and environmental factors [9]. Some of the factors that might contribute to CRS are allergic sensitization, asthma, genetic factors (i.e. cystic fibrosis), local eosinophilia, and the presence of local colonizing bacteria such as *Staphylococcus aureus* or fungi [8].

The societal burden of CRS is significant [9]. Studies have identified that CRS affects up to 14% of the adult population in United States [9]. A Canadian study has reported up to 5% prevalence rate for CRS in Canada [10]. The prevalence of CRS is higher for women and increases with age [10]. Additionally, the prevalence is higher in individuals with history of allergy or asthma, and individuals with chronic obstructive pulmonary disease [10]. CRS affects both mental and physical health of patients and decreases their functioning in society [9,10]. Further, the economic burden of CRS is significant, since patients have higher utilization of health care resources such as diagnostic tests, medical and surgical therapies [10]. It has been shown that patients with CRS experience significantly greater physical pain, and less social function compared to patients with other chronic diseases such congestive heart failure, angina pectoris, chronic back pain, and chronic obstructive pulmonary disease [11]. In order to measure the impact of CRS on patient’s quality of life, a disease-specific quality of life metrics called 22 items Sinonasal Outcome Test (SNOT-22) has been developed [12]. SNOT-22 is a valid instrument that contains 22 questions covering topics related to emotional consequences, functional limitations and physical problems [12].

CRS is a challenging disease to manage due to the lack of complete knowledge about the factors contributing to its development and persistence [10]. Further, the safety and efficacy of different therapies have not been rigorously studied in clinical trials [10].

The first step in providing care for patients diagnosed with CRS is to identify and assess some of the contributing factors [10]. The goal of treatment for patients with CRS is to reduce their symptoms by decreasing the inflammation and controlling any underlying infections [10]. The intranasal treatment includes regular use of saline irrigation and corticosteroids [13]. The other treatment options are: oral corticosteroids, antibiotics, and endoscopic sinus surgery if refractory symptoms are present [13]. Additionally, there are ongoing research about the efficiency of biological agents such as monoclonal antibodies against inflammatory mediators such as IgE, interleukin-4 (IL-4), and interleukin-5 (IL-5) [13].

Difficult-to-treat, or recalcitrant CRS is defined by EPOS (European Position Paper on Rhinosinusitis and Nasal Polypos) as patients who have persistent symptoms despite receiving appropriate medical, and surgical therapy [3]. There are variety of underlying factors that should be considered in patients with recalcitrant CRS that may contribute to the persistence or recurrence of CRS [2]. Some examples of these factors include: Asthma, cystic fibrosis, immune dysfunction, ciliary dyskinesia and anatomic variation [2]. Early identification of such contributing factors is critical in selecting the most appropriate treatment options for patients suffering from recalcitrant CRS [2].

**Cystic Fibrosis (CF)**

Cystic fibrosis (CF) is an inherited disorder that impacts children and young adults in an autosomal recessive fashion [4]. The frequency of CF is different among various ethnic groups, with the highest prevalence being in individuals from Northern European ancestry [4]. CF develops as a result of mutations in the gene coding for the cystic fibrosis transmembrane regulator (CFTR) [4]. CFTR is expressed on the apical cell membrane throughout the body and functions as a chloride ion channel [5]. Therefore, this mutation causes dysregulation of water and electrolytes in CF patients, and affects exocrine (secretory) organs such as lung, liver, gut, pancreas and sweat glands [5]. The pulmonary manifestations have been identified as the main cause of morbidity and mortality in CF patients [5]. As a result of CFTR dysfunction, and unregulated absorption of ions and water across the epithelium in the respiratory tract, the secretions become sticky and thick [4,5]. These results in the failure of the normal mucociliary clearance, obstruction of the airways, and defective immune mechanisms against bacterial infections such as *Pseudomonas* that lead to decrease in overall lung function [5].

Criteria for CF diagnosis are based on the presence of one or more clinical presentations plus at least one evidence of CFTR dysfunction [14]. The clinical presentations of CF include positive new born screening (NBS), family history of CF (mostly siblings), and signs and/or symptoms of CF [14]. Some of the CF presenting symptoms can include pancreatitis, respiratory symptoms, chronic sinusitis, obstructive azoospermia, intestinal manifestation and metabolic disorders [14]. The evidence for
CFTR dysfunction may include: elevated sweat chloride above or equal to 60 mmol/L, presence of 2 CF-causing CFTR mutations on separate alleles, and CFTR physiologic testing which include abnormal Nasal Potential Difference (NPD) or intestinal current measurements [14]. According to the criteria for CF diagnosis, in order to assess the dysfunction of CFTR, sweat chloride test is the gold standard and should be performed first, followed by blood analysis for CFTR genetic mutations, and lastly CFTR physiologic tests [14].

During the sweat chloride test, the sweat glands are stimulated with pilocarpine (a parasympathetic stimulant) by iontophoresis on arm and/or back [15]. The sweat is collected and the sodium, chloride, and/or conductance are measured [15]. In CF patients, the salt concentration of the sweat is higher compared to non-CF patients, due to the deficient CFTR in sweat ducts that leads to failure of chloride and sodium reabsorption [15]. Sweat chloride concentration is used for CF diagnosis, since it is considered to be more reliable compared to sodium concentration in sweat [15]. Sweat chloride concentration below 30 mmol/L is normal and suggests that CF is unlikely [14]. Chloride concentration in the intermediate range of 30-59 mmol/L suggests that further analysis is needed to rule out CF and concentration above or equal to 60 mmol/L is suggestive of CF [14]. To ensure the accuracy of results, sweat chloride testing should be performed according to the approved procedures such as The Cystic Fibrosis Foundation Guidelines [16].

There has been over 1900 CFTR mutation identified, many of which do not cause CF [5]. The mutations vary in the effect they have on CFTR function and therefore the clinical severity [5]. Severe lung diseases result from mutations that reduce the CFTR activity significantly [5]. CFTR mutations have been grouped into six classes (I-VI) based on their effect on gene expression [5]. Classes I and II mutations lead to severe lung disease as they result in little or no CFTR function because of transcription errors and defective protein maturation respectively [5]. Classes III, IV, and V mutations have increased level of residual CFTR function, and therefore result in milder phenotype with maintenance of pancreatic sufficiency [5].

CFTR2 (Clinical and Functional Translation of CFTR) project provides the details of phenotypic consequences of CFTR variants by collecting clinical and laboratory evidences [17]. Majority of patients will be diagnosed with CF as a new born or in young age with the utilization of NBS [18]. However, the diagnosis of CF in adults has been increasing based on our enhanced understanding about the variability in the clinical phenotypes, age of onset and the degree of disease severity in CF patients [18]. According to 2018 Canadian CF Registry Annual Data Report, 60% of the individuals were diagnosed with CF before the age of one year, and 73.4% were diagnosed before the age of two years [19]. Adults who were diagnosed with CF later in life (18 years or older) accounted for 7.7% of all the diagnosis in 2018 [19]. The diagnosis of CF in adults has been linked to mutations that lead to residual function of CFTR, and therefore result in delayed onset and lesser severity of the disease [18]. Adult patients often present with clinical symptoms, and it is relieving for them to be diagnosed with CF which allows them to have access to evidence-based approach to care [18]. Further, the diagnosis would allow the patients to notify their family members who might be potential carriers [18]. Significant benefits have been observed in the lung function of the CF patients who were diagnosed in adulthood after the initiation of conventional CF therapy [18].

The Connection between CRS and CF

Based on the unified airway model, the entire respiratory system is a single functional unit where the diseases of the upper airway affect the lower airway, and vice versa [20]. Since the epithelium and mucosa in the upper and lower respiratory airways are uniformly subjected to the same inflammatory and infectious factors, it has been suggested that CF represents a bidirectional pathological process [20].

Majority of the patients with CF develop CRS due to mucostasis resulting in mucous-filled infected sinuses and subsequent inflammation of the sinonasal mucosa [20]. CRS has been reported in 30% to 67% of patients with CF over all age groups [2]. In a study conducted by Berkhurst et al., 62.5% of patients with CF met the EPOS diagnosis criteria for CRS, and the prevalence of nasal polyps among these patients was 25% [21]. However, it has been noted that CF patients underreport CRS symptoms, with only 10-15% explicitly complaining of sinonasal symptoms [20]. The reason is unclear and may be because of acclimation to chronic disease or due to less severe CRS symptoms compared to CF-related symptoms [20]. Additionally, Berkhurst et al. found that patients with class I-II CFTR mutations had significantly smaller frontal and sphenoid sinuses, more opacification in the sinonasal area and more osteitis/neoosteogenesis of the maxillary sinus wall relative to patients with Class IV and V mutations [21]. These features of CRS might assist in distinguishing patients with CF compared to non-CF patients on radiography.

Additionally, increased mutation of CFTR genes have been observed in patients with CRS. A case-control study was conducted by Wang et al. to determine the relationship between CFTR mutation and CRS by recruiting 147 adult patients with CRS and 123 CRS-free white control subjects [22]. They examined the genomic DNA samples extracted from the blood of participants for the presence of 16 mutations known to cause 85% of CF alleles in the general white population [22]. This study found that the prevalence of a CF mutation in patients with CRS was 7% which was significantly higher than the control group where the prevalence was 2% [22]. Based on their results, they concluded that the mutations in CFTR gene may be associated with the development of CRS in adult patients [22]. In another study conducted by Raman et al. 58 white children with CRS were recruited that did not meet the diagnostic criteria of CF and underwent sweat chloride testing and genotyping for CFTR mutations [23]. They used an assay that looked for 87 CFTR mutations that accounts for 90% of all the CF mutation seen in individuals of northern European ancestry [23]. Their results showed that 7 children (12.1%) with CRS had CFTR mutations, compared to the expected rate for this ethnic group which is 3% to 4% [23]. Only 1 of the 7 children had a borderline abnormal sweat test [23]. They concluded that there is an increased prevalence of CFTR mutations in children with CRS who do not meet the diagnostic criteria for CF, usually in the setting of normal sweat chloride test results [23].
Conclusion and Future Studies Direction

Based on the previous research, CFTR gene mutation might play a role in the development of CRS. However, limited research has been conducted to determine the prevalence of undiagnosed cystic fibrosis (CF) in adult patients with recalcitrant chronic rhinosinusitis (CRS). To conduct this research, we recommend a cross-sectional observational study, where adult individuals who have been diagnosed with recalcitrant CRS based on the diagnostic criteria are recruited. The recruited patients should undergo sweat chloride testing to assess the CFTR dysfunction. The patients with sweat chloride concentration above and/or equal to 30 mmol/L will be directed for CF genetic testing analysis by blood tests to confirm their diagnosis. We hypothesize that the prevalence of CF is higher in adult patients with recalcitrant chronic rhinosinusitis (CRS) compared to the expected rate in the general population.

This area of research needs attention, since patients who suffer from recalcitrant CRS with identifiable CFTR dysfunction may benefit from CF-targeted therapies. Traditionally, treatment of CF was based on management of symptoms that result from CFTR dysfunction [24]. However, newly developed drugs named CFTR modulators are available that improve or restore the function of mutant CFTR protein [24]. These drugs are available for CF patients with certain CFTR mutations [24]. Some of the currently available CFTR modulators are: Ivacaftor, lumacaftor, and tezacaftor [25]. CFTR modulators have been shown to be highly effective [26]. A research conducted by Sawicki et al. showed that with ivacaftor the rate of pulmonary decline decreases by nearly 50% over a 3-year period in CF patients [26]. Ivacaftor is a potentiator of CFTR protein and increases the open time of the channel [25]. It is used in the treatment of subset of cystic fibrosis patients with G551D mutation, which is a class III mutation that leads to decreased open time of the CFTR channel as a result of diminished adenosine triphosphate (ATP) binding and hydrolysis [25,27]. A recent study conducted by McConnell et al. assessed the impact of ivacaftor on the quality of life related to sinus disease using SNOT-20 questionnaire in CF patients with G551D mutation [27]. Their results showed significant improvement in subset domains of SNOT-20 including rhinologic QOL (quality of life), sleep QOL, and psychological QOL subsets over 3 follow-ups at 1-month, 3-month, and 6-month after starting ivacaftor therapy [27]. These results provide promising evidence that CFTR-modulators can be a possible avenue in the management of CF CRS patients. Therefore, the diagnosis of CF in patients with recalcitrant CRS would benefit the patients by optimizing their treatment management.

REFERENCES

