

Rhinosinusitis and Comorbidities

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Abstract A variety of systemic conditions impact the incidence, severity, prognosis, and treatment approach in patients with chronic rhinosinusitis (CRS). The controversy surrounding the impact of allergic rhinitis on CRS continues, but it is reasonable to consider and treat allergic sources of inflammation in any patient with CRS. CRS is more severe in patients with aspirin sensitivity but improves—at least temporarily—to the same degree as in non-aspirin-sensitive patients, given appropriate therapy. Polypoid rhinosinusitis in cystic fibrosis patients is characterized by compromised mucociliary clearance and infection with staphylococcal and pseudomonal organisms. Affected individuals require frequent antibiotic treatment, saline lavage, and repeated surgeries. Rhinosinusitis is among the most common infectious complications of humoral immunodeficiency, which is not uncommon in patients with refractory CRS. The treatment approach in immunodeficiency includes aggressive antibiotic treatment and intravenous immunoglobulin. Specific diagnosis of comorbid systemic conditions with CRS will facilitate appropriate management.

Keywords Chronic sinusitis · Allergy · Aspirin sensitivity · Immunodeficiency · Cystic fibrosis

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Introduction

Chronic rhinosinusitis (CRS) is a term that describes a group of disorders characterized by persistent inflammation of the paranasal sinuses. The pathophysiology of CRS is incompletely understood, and multiple inflammatory, infectious, or anatomic factors may contribute singly or in combination to trigger and sustain the persistent inflammation in CRS. Healthy paranasal sinuses depend on intact immunity, a protective mucus blanket, functional mucociliary clearance, and patent sinonasal drainage pathways. Clearly, CRS is not merely the result of anatomic obstruction to sinus drainage; multiple additional factors are involved. To date, the significant progress in defining and classifying CRS has paved the way for important research into the pathogenesis and treatment of CRS.

At this stage of our understanding, most cases of CRS seem to be idiopathic. However, several systemic disease conditions may contribute to the pathogenesis of CRS. Such systemic diseases may predispose an individual to the development of acute rhinosinusitis or CRS to such a degree that they seem to cause CRS. Even when systemic disease is not a direct cause of CRS, it may alter the prognosis of CRS, lead to more severe disease, or change the applicable treatment paradigm. Among the systemic diseases widely recognized as causes of CRS (ie, diseases that promote the necessary and sufficient conditions for its development) are cystic fibrosis (CF) and aspirin-exacerbated respiratory disease. Indeed, summary statements from a recent multidisciplinary working group consensus report acknowledge that defects in mucociliary clearance, aspirin-exacerbated respiratory disease, and antibody deficiency “predispose” individuals to rhinosinusitis [1]. The causal relationships between other systemic conditions, such as allergy and CRS, are somewhat

controversial. Although new studies are needed to help us better understand the contribution that systemic disease makes to the prevalence and clinical heterogeneity among the population of CRS sufferers, we know that a variety of systemic conditions can cause, worsen, or alter the treatment of CRS. This article discusses recent contributions to the literature on this topic.

Allergy

The role of allergy in CRS is a subject of investigation and controversy. Although allergic inflammation of the sinonasal cavities clearly alters sinonasal physiology (eg, mucociliary clearance, sinus ostial patency) and thus seems to represent a primary etiology of CRS, clear and convincing evidence for a direct cause-and-effect relationship between allergy and CRS is currently lacking. Ample evidence links “allergic-type” inflammation (ie, the presence of eosinophils IgE and interleukin-4, -5, and -13,) with CRS. Weaker is the evidence of allergic sensitization to environmental aeroallergens associated with type I hypersensitivity among CRS sufferers. Some authors suggest that unidentified antigens, such as occupational agents and bacterial superantigens, or the presence of local nasal allergy without positive skin prick testing (SPT) or detectable serum-specific IgE directed against allergens may explain in part the lower prevalence of “allergy” reported in some studies [2]. Differences in the definition of allergy also may account for discrepancies in reported prevalence. Many authors define allergy as the presence of allergen-specific IgE by SPT or positive serology (ImmunoCap [Phadia, Uppsala, Sweden], radioallergoimmunosorbent testing). This definition excludes many instances in which the inciting antigen cannot be identified despite the appearance of a common inflammatory process. A similar conundrum exists in the conditions collectively known as *eosinophilic gastroenteritis*, in which patients tend to be SPT negative, yet food allergy is considered to be the major cause or inciting agent in these disorders [3]. Institution of an empiric food elimination diet of common food allergens may greatly improve the condition. Similarly, “allergy” may be a cause of the inflammatory disease process in CRS even if we are currently unable to determine the inciting antigens with a diagnostic test. The strength of the evidence linking CRS and allergic disease must be evaluated in this context of unknown predispositional factors among CRS sufferers and inconsistent definitions of allergy among investigators.

Whereas perennial allergic rhinitis predisposes patients to acute bacterial rhinosinusitis, the same cannot be said of its relationship to CRS. The significant symptomatic overlap between allergic rhinitis and CRS renders their

distinct diagnosis difficult and may explain why, especially in children, CRS and allergy have been frequently associated [1]. Late-phase allergic inflammation in response to airborne allergens may in fact contribute to the inflammation seen in CRS. On the other hand, in CRS with nasal polyposis, less than half of patients have a positive SPT. Moreover, a positive test for allergy in a patient with CRS does not necessarily mean that a patient has “allergic CRS” (although it has been reported to be a prognostic factor after surgical treatment for CRS in some studies) [1].

Some evidence suggests that allergy predisposes individuals to CRS. For example, there is a high rate of CT abnormalities in allergic patients, and in some studies, CRS patients have a higher incidence of SPT positivity than healthy control populations [4, 5]. Positive supportive evidence for the importance of allergy in CRS could be derived from epidemiologic studies showing that allergies are more common in CRS patients, that allergies are associated with severe CRS, or that allergic patients have a worse outcome with treatment. Such data are lacking in the recent literature. For example, Robinson et al. [6] studied a series of CRS patients undergoing endoscopic sinus surgery (ESS). Only 30% of these patients had serologic evidence of atopy, which the authors claimed was below the 45% rate for the overall healthy Australian population. Allergic sensitization did not influence symptom severity, CT staging scores, or likelihood of revision surgery. These results agree with those of another recent cohort study that did not show a more severe disease or worsened treatment outcome in sensitized versus non-sensitized patients who were surgically treated and observed for more than 1 year [7]. Gelincik et al. [8] reported on the evaluation of CRS and asthma in a consecutive series of patients evaluated in an allergy clinic. They did not find an increase in CRS or asthma in allergic compared with nonallergic patients as assessed by SPT. Additionally CT scores did not differ by allergic status [8]. Similarly, Pearlman et al. [9] carried out a cohort study of CRS patients subjected to allergy and asthma evaluation; about half of the CRS patients had positive SPTs, and there was no association between positive SPT status and severity of CRS. Thus, in cross-sectional studies of surgical and nonsurgical CRS patients, positive allergy tests do not correlate with disease severity.

These studies conflict with prior reports that found that allergic sensitization is significantly more common in CRS patients undergoing ESS or that allergic status affects outcomes [10]. Moreover, caution must be taken in interpreting the results of studies using convenience sampling of cases referred for surgical intervention. The prevalence of allergic sensitization in patients referred for surgery may vary greatly in many uncontrolled factors (eg,

prior medical therapy). Thus, although many questions remain about the importance of allergy in CRS patients, and much remains to be resolved from the findings of various investigators, it is the authors' opinion that allergy should be considered among the factors that may be contributing to the sinonasal inflammation in patients with CRS, and that specific and nonspecific allergy therapy should be used as a means to ameliorate any contribution that this particular inflammatory mechanism may be making to the overall sinonasal inflammation in CRS patients.

Aspirin Sensitivity

Aspirin-exacerbated respiratory disease, also known as aspirin triad disease, or Samter's triad, is an adult-onset disorder of rhinosinusitis, nasal polyposis, and asthma. Urticaria, angioedema, and anaphylaxis are additional clinical manifestations in some individuals. Symptoms may be triggered by aspirin or NSAID exposure; this forms the basis of the test that confirms the diagnosis: oral challenge with aspirin. The pathogenetic mechanisms of aspirin sensitivity are incompletely understood but seem to include an overproduction of proinflammatory cysteinyl leukotrienes and prostaglandin D₂ and a reduction in the production of anti-inflammatory prostaglandin E₂, which leads to predominantly eosinophilic inflammation [11•].

Although the role of allergy in the pathogenesis of CRS remains controversial, the causal relationship between aspirin sensitivity and CRS with nasal polyposis has achieved widespread acceptance. Evidence clearly demonstrates that aspirin-sensitive patients have a particularly severe form of disease that is vulnerable to recurrence despite appropriate medical and surgical management. About 20% of all patients with CRS with nasal polyposis have aspirin sensitivity [12••]. Medical management consists of avoidance of salicylates and NSAIDs, use of leukotriene modifiers (montelukast, zafirlukast, zileuton), topical and systemic corticosteroids, and in some cases aspirin desensitization therapy [13].

Patients with severe nasal polyposis are frequently treated surgically. A recent prospective cohort study of patients undergoing sinus surgery showed that aspirin sensitivity predicted a poorer outcome after ESS in terms of quality of life and endoscopy score [7]. Aspirin-intolerant patients had worse presurgical CT and endoscopy scores. Reanalysis in the wake of longer follow-up revealed that aspirin-sensitive patients improved to a similar degree as other CRS patients after ESS, but aspirin-sensitive patients had comparably worse disease after treatment [14]. This increased severity has been highlighted in recent publications. For example, Kim and Kountakis [15] reviewed 208 consecutive patients undergoing ESS and

found that aspirin-sensitive patients had undergone ten times as many sinus surgeries as non-aspirin-sensitive patients in the cohort. In sum, aspirin-sensitive patients with CRS have more severe disease and are more likely to require multiple endoscopic surgeries to manage their disease. Given the refractory and recurrent nature of CRS in aspirin-exacerbated respiratory disease, intensive medical management that goes beyond the usual management with corticosteroids and leukotriene modifiers is important. Every effort should be made to control concomitant allergic inflammation through avoidance and immunotherapy [11•]. Additionally, aspirin desensitization has been shown to decrease the need for revision ESS and should be considered in patients with aspirin-exacerbated respiratory disease with a history of multiple sinus surgeries [16].

Cystic Fibrosis

CF is an autosomal recessive disease caused by mutations of a gene on chromosome 7q31 with resultant defective chloride channels, increased mucus viscosity in the respiratory and gastrointestinal tract, secondary infection, inflammation, sinus blockage, and polyp formation. CF mucus is 30 to 60 times more viscous than normal mucus, leading to severe dysfunction of mucociliary clearance in the sinonasal cavities. When sinusitis develops, *Pseudomonas* and *Staphylococcus aureus* are the organisms most frequently cultured. DNA from neutrophils recruited to the infected tissue further increases the viscosity of secretions. Elevated salt content in sweat suggests the CF diagnosis. Up to 5% of the Caucasian population carries the gene, and one in 20,000 infants are affected. Nasal polyposis is rare in children but may be present in 5% to 86% of children with CF [17]. Most patients with CF have chronic sinus inflammation regardless of symptoms. Interestingly, the sinonasal consequences of the CF mutation may not be confined to homozygotes with two abnormal genes. In a case-control study of CRS patients, 7% had a CF mutation, whereas non-CRS controls had a 2% rate of mutation of one allele [18]. This suggests that in some patients, heterozygosity for a CF gene may be a contributing factor in the development of CRS [18]. In a later study by the same investigators, 53% of CF carriers self-reported CRS using a survey study, again suggesting that CF carrier status may predispose for the development of CRS [19]. Recently, a genome-wide screen of a small population of related Hutterites with CRS found a strong linkage in the 7q region, suggesting that a locus in this region influences disease susceptibility. Interestingly, this region also includes the CFTR locus, although only one patient had an identifiable polymorphism of the *CFTR* gene [20]. Abnormalities of the CF gene or related loci may be important in

the pathogenesis of some cases of CRS, even in individuals without the CF phenotype.

The goals of medical and surgical management of CRS occurring in patients with CF are the same as for other forms of CRS. However, the disease process and treatment differ for CF/CRS sufferers due to higher rates of *Pseudomonas* colonization, greater need for topical intranasal irrigations, and the potential benefit from topical DNase therapy [21]. The characteristic findings of rhinosinusitis in CF patients also may impact the surgical approach: the lateral nasal wall is frequently distorted, the frontal and sphenoid sinuses may be hypoplastic, and mucocoeles are not uncommon. The polyps in CF patients have a propensity for recurrence, and the sinonasal mucosa usually fails to normalize after relief of obstruction [17, 22]. Keck and Rozsasi [23] reported that complete remission of nasal polyposis was only seen in 31% of patients after surgery. Rowe-Jones and Mackay [24] reported on a cohort of 46 patients who underwent 85 endoscopic surgeries and found that patients had a 50% chance of returning to their preoperative symptom state or of requiring a second operation within 18–24 months of follow-up. The median interval between sinus surgeries in one small series with prolonged follow-up was 4 years (range, 18 months–6.5 years) [22]. Citing this propensity for recurrence, Shatz [25] noted that more extensive, permanent sinus drainage procedures provided longer-lasting results. However, overall, surgical treatment usually offers only transient benefit in patients with CF/CRS. With the median survival for CF increasing, there is a greater need for intervention to improve quality of life. Surgery in CF/CRS is indicated for medically refractory polyposis, nasal obstruction, pulmonary exacerbations associated with sinusitis, in anticipation of transplant, and for mucocoeles. Although attempts have been made to correlate CF genotype with clinical course and the need for revision sinus surgery, a recent review of a large series of surgical cases found no correlation between CF genotype and the need for revision sinus surgery or number of sinus surgeries [26]. Thus, it is not yet possible to predict the clinical course of CRS in CF patients.

Until recently, no available studies had compared CF with non-CF patients with CRS, but it appears the symptoms of CRS may not be more severe in CF patients, although these patients are more likely to suffer from recurrent polypoid rhinosinusitis. Interestingly, CF patients with CRS experience the same quality-of-life improvements as other polypoid CRS patients after ESS [27].

Immunodeficiency

Sinusitis is one of the most common complications of immunodeficiency. Local secretory or systemic humoral

immunodeficiencies in particular seem to predispose individuals to CRS. Other forms of immunodeficiency (eg, lymphopenia or neutropenia) are more important in the pathogenesis of acute forms of rhinosinusitis, such as acute invasive fungal sinusitis. CRS symptom severity may not be impacted by immunodeficiency, but the CRS may be more refractory to the usual treatment approaches. Sinus abnormalities seem to be common in humoral immunodeficiency. CT findings of chronic sinusitis were detected in 41 of 45 patients with agammaglobulinemia and common variable immunodeficiency (CVID), a heterogeneous group of disorders characterized by panhypogammaglobulinemia and recurrent infections [28].

Some patients with hypogammaglobulinemia may harbor bacteria or viruses in their sinuses and have unrecognized, subclinical CRS [29]. Not uncommonly, humoral immunodeficiency is uncovered only after a patient has been treated over a period of years with multiple sinus surgeries. Correct diagnosis is important because the presence of immunodeficiency may alter the recommended course of treatment: antibiotic prophylaxis; early, aggressive, culture-directed antibiotic treatment; and the use of agents such as intravenous immunoglobulin (IVIG) [30]. Early diagnosis and institution of IVIG replacement therapy for agammaglobulinemia and CVID reduce the prevalence of CRS, whereas delayed administration does not seem to reverse some of the chronic predisposing factors in CRS.

Chronic or recurrent sinusitis is the most common clinical presentation of patients with CVID [31]. In a large cohort of CVID patients, the prevalence of “chronic sinusitis” varied from 36% to 54% [32•]. In this cohort, the prevalence of chronic sinusitis increased despite treatment with IVIG. In X-linked hyper-IgM syndrome, sinusitis is second only to pneumonia as the most common infectious complication [33]. Inadequate antibody response to polysaccharide antigens (*Pneumococcus*) may occur in patients with normal serum immunoglobulin concentrations. In a series of 75 patients with this condition, recurrent respiratory infections such as otitis, sinusitis, bronchitis, and pneumonia were present in 92% of patients [34].

The rate of immunodeficiency in refractory chronic sinusitis cases is unclear. The definition of refractory CRS is variable in the literature. Although immunodeficiency is probably more common in CRS patients than in the general population, the true prevalence is unclear. Chee et al. [30] reported on 79 patients with refractory rhinosinusitis, defined by at least one previous sinus surgery and/or three episodes of objectively documented rhinosinusitis in the previous year, referred from the otolaryngology clinic to the allergy/immunology clinic at a large tertiary care medical center. On average, this group had 2.94 prior sinus surgeries. A large percentage of these individuals had positive allergy tests, low total IgG, low IgA, or low IgM.

About 10% to 50% had abnormalities on cell-mediated immunity tests, and 10% of patients had CVID. In a similar study, Vanlerberghe et al. [35] reported a 22% prevalence of humoral immunodeficiency in a cohort of patients with “refractory rhinosinusitis.” This study found that although humoral immunodeficiency was not uncommon in patients with refractory rhinosinusitis, most of these were subtle IgG subclass deficits, whereas the more severe humoral immune disorders were rare. However, measurement of serum IgA, IgG, and IgG subclasses should be part of the evaluation of patients with refractory rhinosinusitis, with further work-up as indicated.

Conclusions

A variety of systemic conditions may impact the prevalence, severity, and treatment of CRS. In some cases, these conditions justify being labeled as distinct subtypes of CRS. For other conditions, such as allergy, further research will be required to further characterize the linkage with CRS. Physicians need to consider the impact of these conditions on the treatment and prognosis of their patients.

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