SCUAD and chronic rhinosinusitis. Reinforcing hypothesis driven research in difficult cases*

Emmanuel P. Prokopakis1, Ioannis M. Vlastos1, Berrylin J. Ferguson2, Glenis Scadding3, Hideyuki Kawauchi4, Christos Georgalas5, Nikolaos Papadopoulos6, Peter W. Hellings5,7

1 Department of Otorhinolaryngology, University of Crete School of Medicine, Heraklio, Crete, Greece
2 Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, USA
3 Department of Allergy and Medical Rhinology, Royal National TNE Hospital, London WC1X8DA, United Kingdom
4 Department of Otorhinolaryngology, Shimane University, Faculty of Medicine, Izumo, Japan
5 Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam
6 Department of Peds-Allergology, University of Athens, Greece
7 Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium

Abstract

Background: Our objective is to present recent research findings on recalcitrant chronic rhinosinusitis (CRS) in relation to “Severe Chronic Upper Airway Disease” (SCUAD).

Methodology: Literature review using Medline and Embase databases (search terms ‘chronic rhinosinusitis’,”chronic sinusitis” or “Severe Chronic Upper Airway Disease”) limited to articles published in the English language.

Results: Complex pathophysiological mechanisms characterize various forms of chronic rhinitis and rhinosinusitis (CRS), where inflammation persists in spite of adequate medical treatment. In these cases, a multifactorial etiology often underlies the development of sino-nasal inflammation. The interaction between chronic upper and lower airway inflammation via neurogenic and systemic pathways may complicate the therapy of these patients, and lead to insufficient symptom control.

Conclusion: The recently introduced definition of “Severe Chronic Upper Airway Disease” (SCUAD) increases awareness of those patients with persistent inflammation and symptoms despite guideline-driven pharmacologic treatment. The concept of SCUAD may prove helpful in directing research towards clarifying the definition, diagnosis and pathophysiology of rhinitis and rhinosinusitis, their limits and overlap. In this review, a hypothesis on SCUAD immunopathology is also presented.

Key words: chronic rhinosinusitis, severe chronic upper airways disease, definitions, pathophysiology

Introduction

Severe Chronic Upper Airway Disease (SCUAD) is a term recently introduced by Bousquet et al. [1] defining those patients with allergic (AR), non-allergic (NAR), and occupational rhinitis (OR) and chronic rhinosinusitis (CRS) with and without nasal polyposis, whose symptoms are inadequately controlled despite pharmacological treatment following international validated guidelines, such as ARIA [2,3] and EPOS2012 [4]. Chronic inflammatory disorders of the upper airways are extremely prevalent and have a major impact on public health and the socioeconomic state [2,31]. It is estimated that up to one third of rhinitis and rhinosinusitis patients present with persistent inflammation and/or symptoms despite adequate treatment [2,4]. In other words, a great number of these patients fail to respond to treatment options suggested by guidelines such as antibiotics, steroids or surgery. Moreover, these disorders commonly complicate diagnosis and management of diseases of the lower airways. The group of SCUAD patients is a subgroup of patients that challenge the currently
available treatment schemes and stress the importance of re-
search in the field of difficult to treat rhinitis and rhinosinusitis
patients.

Although rhinitis is not a life-threatening disease, patients with
this condition and especially those with SCUAD have a severely
impaired quality of life \[^{31}\]. Moreover, patients with CRS have
more bodily pain and worse social functioning than patients
with chronic obstructive pulmonary disease (COPD), congestive
heart failure, or back pain \[^{36}\]. CRS represents a significant health
problem, resulting in frequent surgical procedures and a large
financial burden on society \[^{36}\]. Despite recent clinical and basic
research efforts, the pathophysiology of the disease is only
beginning to be understood. Current research has reinforced
the belief that CRS is a multifactorial disease process involving
genetic, environmental, occupational, anatomic, iatrogenic and
immunological factors \[^{17}\]. Based on the concept of “united air-
ways”, new diagnostic and therapeutic approaches are required
to delineate whether intermittent and persistent inflammatory
disorders of the upper airways represent a common disease
with strong relationships with asthma and other diseases, or are
distinct entities that interact with each other or are simply being
confused because of common symptoms (Figure 1). The scope
of this review is to highlight the arguments and evidence on
each of the aforementioned hypotheses and how these relate to
SCUAD, to reinforce clinical and basic research towards a better
delineation of these issues.

SCUAD
Definition issues
Attempts have been made to define rhinosinusitis in terms of
pathophysiology, microbiology, radiology, severity and duration
of symptoms \[^{18-20}\]. However, the predictive value of the symp-
tom-based definition of CRS, commonly used in epidemiological
studies, falls behind that which includes objective tests \[^{113}\]. The
EP3OS document \[^{10}\] offers definitions for clinical and research
use, as well as for epidemiological studies. Despite the initial
results showing that symptom-based CRS is significantly asso-
ciated with positive endoscopy and with self-reported doctor-
diagnosed CRS \[^{12}\], further adjustments are needed because
they have a moderate reliability over time \[^{12}\]. Moreover, a more
recent study \[^{132}\] questioned whether these definitions evaluate
the same disease due to their moderate agreement.

In addition, signs and symptoms of allergic and non allergic
rhinitis overlap. These entities are routinely differentiated by
the presence or absence of an overt IgE- mediated pathogenic
mechanism, however local IgE may be relevant \[^{14}\].

Related etiological factors
Despite previous studies suggesting that there is an increased
incidence of acute and chronic rhinosinusitis in patients with
allergic rhinitis \[^{15-17}\] more recent evidence suggests that al-
lergic rhinitis is an associated condition rather that a trigger for
CRS \[^{14}\]. Several mechanisms have been studied regarding the
pathophysiology of rhinosinusitis in association to allergic and
non-allergic rhinitis, such as the role of mucociliary clearance.
However, the role of sinonasal cilia, their response to environ-
mental stimuli and their function under several conditions
remains unclear \[^{119,20}\]. For example, cystic fibrosis (CF) and pri-
mary ciliary dyskinisia (PCD) both cause disturbances of mucoci-
lary clearance and are commonly implicated in difficult-to-treat
CRS cases. Nevertheless, CF, unlike PCD \[^{21}\], often presents as CRS
with nasal polyps and is associated with infection and biofilms,
indicating the existence of complex molecular and biochemical
mechanisms that are incompletely understood. The current
development of nasal and lung biomarkers, such as nitric oxide
\[^{22}\], for the differential diagnosis of those diseases signifies the
importance of further basic and translational research studies.
The reverse interaction, namely the impact of microbial coloni-
ization and/or environmental agents on allergic and non-allergic
rhinitis remains incompletely understood. Microbial infections
and bacterial products, such as Staphylococcus aureus enteroto-
xin B have been implicated in inflammatory responses \[^{23}\], and
have been shown to facilitate allergic sensitization \[^{24}\]. However,
the complexity of the issue can be seen by the studies on the
hygiene hypothesis \[^{25}\]. Bacterial, viral or other infectious factors
modulate T-cell responses differently and time of exposure can
modulate the outcome. Several molecules and mechanisms
are being investigated. For example, the expression of innate
immune markers, such as Toll-like Receptor-9 (TLR9), has been
shown to be upregulated in response to repeated microbial
insults \[^{26}\]. TLRs are implicated in the hygiene hypothesis and
several experimental (with TLR agonists), genetic (mostly in rela-
tions to TLR polymorphisms) and epigenetic data are now avai-
able. However, information gathered on the issue is insufficient
for robust verification of the vicious cycle theory reported in
Figure 1. In other words, unless the complexity of the molecular
interactions between assaulting factors and immunological host
responses as well as their biochemical consequences is resolved,
the hypothesis that Severe Chronic Upper Airway Diseases are
casted by a dysfunction of the feedback mechanism in some
patients, cannot be supported.

A single disease?
Multiple pathophysiological pathways involving innate and
adaptive immune responses, specific cytokine profiles, molecu-
lar mechanisms at the level of epithelial cells, surface, microen-
vIRONMENT or intracellular matrix have been found in common in
allergic and non-allergic rhinitis and CRS. A hypothesis that can
be generated is that the minority of patients with allergic rhini-
tis, non-allergic rhinitis and CRS, who have symptoms refractory
to standard medical therapy and sinus surgery procedures, may
have a common underlying pathophysiological condition that presents as Severe Chronic Upper Airway Disease. The “united airways concept” (Figure 2) implies that besides the anatomical continuity of the upper and lower airways, inflammation in one part of the airway influences the homeostasis of the other [27]. The mechanisms underlying this interaction have been studied primarily in allergic disease, showing systemic immune activation, induction of inflammation at a distance, and a negative impact of nasal inflammation on bronchial homeostasis [27]. In addition to allergy, the concept of global airway disease has been demonstrated among others in patients with non-allergic asthma and in those with COPD who present with sinonasal symptoms and inflammatory markers in nasal lavages [28]. To further expand the idea of a broader causal mechanism the term allergic rhinosinusitis has been adopted by some authors [29]. Several hypotheses have been vigorously debated during the past decade with the majority of studies implicating fungi, biofilms and superantigens in the pathogenesis of CRS. Several of them have been influenced by analogous studies on asthma. A T-cell–driven, non-IgE–mediated hypersensitivity response that culminates in the attraction and specific targeting of eosinophils against colonized fungi in the nasal lumen of CRS patients, with subsequent degranulation and mucosal damage, has been proposed as a possible mechanism of CRS [30]. This hypothesis, the so-called fungal hypothesis, which strongly relates allergic rhinitis, non-allergic rhinitis and CRS, suggests that high levels of Alternaria trigger the accumulation of peripheral blood mononuclear cells and eosinophils. Still, evidence is lacking if this is a disease-specific response or whether Alternaria has any relevance to the establishment of CRS [31]. Moreover, new culture techniques revealed that the percentage of positive fungi cultures was the same in normal controls and in CRS patients [32]. Finally, later clinical studies examining the effect of topical antifungal agents were disappointing [33,34]. Immune responses are being implicated also in the superantigen (SAg) hypothesis, which incorporates biofilm formation and toxin secretion mainly by S. aureus. The biofilm has been described as an aggregation of microorganisms embedded in a protective self-produced polysaccharide matrix. According to the superantigen hypothesis, S. aureus protected by biofilms or sequestered within epithelial cells secrete toxins that result in a generalized stimulation of T cells, cytokine release, and a local polyclonal IgE response, all of which stimulate eosinophil recruitment and the clinical and histopathological changes associated with polypoid CRS [31]. Although about half of CRS with nasal polyposis patients show evidence of Streptococcal Ag responses, multiple pathophysiological pathways likely exist for the development of CRS. This is an evolving field of knowledge and even the role of biofilms is being disputed lately by researchers who believe that the biofilm in the nose and paranasal sinuses is “nothing else but regular respiratory mucosal blanket, a part of the mucociliary system itself, and containing variable number of bacteria” [35]. In terms of therapeutic implications, further research is required to clarify whether prophylactic anti-
bacterial treatment should differ between primary and revision sinus surgery. Moreover, accumulated data on the pathophysiology of CRS have led some researchers to propose SAgs as disease modifiers (Figure 3). The depicted immune barrier hypothesis acknowledges CRS as a member of a family of chronic inflammatory disorders that occur at sites of interface with the outside world. Antigen passage and processing across the nasal epithelium is promoted by defects of the mechanical and innate immune protective barrier that leads to the generation of the chronic inflammatory infiltrate observed in CRS (31). As proposed by Kern et al. (37), “variations in the expression of genes that govern critical molecular pathways involved in Th1 vs Th2 response regulation may be the common primary immunodeficiency disease, primary ciliary dyskinesia or cystic fibrosis can contribute to a constant Th1 activation, that favors tissue remodeling and fibrosis seen in patients with CRS without nasal polyps. Likewise, environmental pollutants and allergens in “susceptible individuals” elicit a Th2 response. The Th2-biased mucosal inflammation, in turn, favours the programming of M2 macrophages within the polyp tissue in CRS with nasal polyps (40) and may contribute to polyps formation. This process can be further violated by a deficiency in T regulatory cells or deregulation in cytokines production, like IL-2 or IL-5, attributed to several genetic and epigenetic factors. Overwhelming data have also been published on the epithelial expression of cytokines that regulate Th2 cytokine responses (i.e., thymic stromal lymphopoietin, IL-25, and IL-33). To further complicate the issue, multiple pathways are involved in the interaction between T cells and other immune cells, like eosinophiles, dendritic cells and baseophils, seen in rhinitis patients (i.e. CRTH2 antagonism is currently being studied as a new therapeutic approach for allergic patients (41,42)). An example of the complex inflammatory response in allergic rhinitis is reviewed in (43). In SCUAD, however, chronic, constant and serious inflammation leads to alternation of expression and concentration of cytokines, ligands, receptors, etc, that obscure the primary deficiency.

In contrary to SCUAD patients, the majority of CRS, allergic and non-allergic rhinitis cases, that are relatively easily treated, have known extrinsic and intrinsic factors and current therapeutic regimens (i.e. antibiotics, immunotherapy) “alleviate” immune responses. After the exclusion of incorrect diagnoses and specific causes of difficult to treat CRS cases (reviewed in (44) and (45)), such as odontogenic inflammation, a significant percentage of patients is reported as having SCUAD (44). It is of interest that an alternation of cytokines production by epithelial and immune cells, as those reported very briefly in the above paragraphs, can cause a failure of the regulation of Th1 and Th2 responses. Our hypothesis, depicted in Figure 4, is that apart from extrinsic and intrinsic factors that can contribute to a constant inflammation characterized either by Th1 or Th2 predominance, defective pathways involved in Th1 vs Th2 response regulation may be the single or just a simple cause of SCUAD.

Unmet needs and future research directions

CRS refractory to standard medical and surgical treatments is a common and debilitating condition. Disease development remains incompletely understood with multiple pathophysiological pathways being proposed, but still requiring investigation. To delineate factors that contribute to severe CRS, epidemiological, clinical and molecular studies are required. The real prevalence and severity of CRS/SCUAD, as well as its effect on social/professional life and costs should be determined by well conducted epidemiological studies. First of all, an
References