Etiology and pathogenesis of chronic rhinosinusitis

Etiologija i patogeneza hroničnog rinosinuzitisa

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Key words: rhinitis; sinusitis; chronic disease; causauty; diagnosis.

Introduction

Chronic rhinosinusitis (CRS) is defined as inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior, posterior nasal drip) + facial pain/pressure + reduction or loss of smell sensation of smell + either endoscopic signs of polyps and/or mucopurulent discharge primarily from the middle meatus and/or edema/mucosal obstruction primarily in middle meatus, and/or computerized tomography (CT) changes showing mucosal changes within the ostiomeatal complex and/or sinuses from more than 12 weeks 1.

It is an increasingly common cause of patients visits to physicians and the principal diagnosis in nearly 2% of them 2. The prevalence of rhinosinusitis is estimated to be 14% of the global population 3. The location and extent of different rhinosinusitis pathological conditions imply a detailed knowledge of anatomic organization of paranasal sinuses, and the first and foremost of ethmoid sinuses. The structures of the lateral nasal wall and paranasal sinuses fall into two anatomically and physiologically distinct categories: the anterior and posterior ethmoid complex. The basal lamella of the middle turbinate is the distinct separation between the two ethmoid complexes. The ostiomeatal complex (OMC) is a functional entity of the anterior ethmoidal complex that represents the final common pathway for drainage and ventilation of the frontal, maxillary and anterior ethmoid cells. The sphenoid recess is a functional entity of the posterior ethmoid complex that represents the final common pathway for drainage and ventilation of the sphenoid and posterior ethmoid cells. Three clinical entities of CRS may be defined: chronic rhinitis, localized sinusitis and diffuse rhinosinusitis 2.

Chronic rhinosinusitis is a multifactorial disease. Pre-disposing factors can be divided into: local host factors, general host factors and environmental or non-host factors 1, 4.

Local host factors

Anatomic variations

Certain anatomic variations such as concha bullosa, nasal septal deviation and a displaced uncinate process have been suggested as potential risk factors for developing CRS 1, 4. The ethmoid sinus area (OMC) is believed to be a major focus for the initiation of CRS 4. The overall incidence of inflammatory disease in OMC in symptomatic patients is not different between those with and without concha bullosa. However, there were many cases in which an abnormally large middle turbinate appeared to obstruct OMC causing secondary infection of the ethmoid, frontal and maxillary sinuses 5. Sinus disease usually starts in the middle of nasal meatus. Many conditions cause narrow or blocking of this space resulting in retention of nasal secret and poor ventilation. Sometimes very localized areas of contact of opposing mucosal surfaces in these key areas of the anterior ethmoid may lead to such a blockage, which in turn may alter nasal function. If opposing mucosal areas come into intense contact, their ciliary beating either stops or is impeded. The mucus between these contacting areas is no longer transported. This stasis provides an ideal condition for viral and bacterial infection 6. Although OMC is important in CRS, it is not the underlying cause of the disease, and the importance of anatomic anomalies is often overestimated 1, 4, 5. Bhattacharyya 7 has shown that maxillary sinus retention cysts do not reflect persistent obstructive pathology on OMC, and are not associated with potentially obstructive anatomic sinus variations. Some studies suggest that concha bullosa may have a role in CRS etiology, while some other suggest that there is no statistically significant relationship between the presence of a unilateral or dominant concha bullosa and OMC, maxillary and frontal sinus disease 6, 9.

Chronic rhinosinusitis is an important clinical problem in pediatric patients. The characteristics of CRS in children...
are very different from those in adults. Kim at al. have found that agger nasi cell is the most common anatomical variation, followed by septal deviation, Haller cell, concha bullosa, paradoxical middle turbinate, and Onodi cell. However, they have not found any significant relationship between CRS and anatomic variations. Adenoid vegetation may cause nasal discharge that is not necessarily due to sinusitis. We could not find any supportive data for the statement that “the greater the adenoid tissue, the more extensive sinusitis”.

General host factors

General host factors, such as genetic factors and immunodeficiency, significantly increase the potential for the development of CRS.

Genetic factors

The role of genetic factors in some disorders that predispose to CRS is well defined, for example, cystic fibrosis (CF), Young’s syndrome, primary ciliary dyskinesia, congenital immunodeficiency syndrome and MUC8 mucin gene up-regulation. Kennedy mentioned that mutation of the CF genes were significantly more common in patients with CRS than in controls (7% vs. 2%), even after exclusion of a patient with undiagnosed CF. Although the carrier frequency for CF ranges from 3–4% in the general population, the prevalence of mutation in the CF transmembrane conductance regulator (CFTR) among the patients with CRS is unknown. These observations suggest that mutations of genes responsible for CF may be associated with the development of CRS. Chronic rhinosinusitis is a common debilitating disease principally affecting sinonasal epithelial function with a resultant diminution of mucociliary transport. Although primary ciliary dyskinesia is commonly associated with CRS, little is known about how this process affects the sinonasal epithelial ciliated cells.

Mucus secretion by both goblet cells and submucosal gland cells is one of the most important defense mechanisms in the nose and paranasal sinuses. However, excessive mucus production characterizes upper airway diseases such as CRS and allergic rhinitis. The major macromolecular constituents of mucus are mucins, which are highly glycosylated proteins. The amount of mucus produced in the human airway is mainly balanced by the rate of production and clearance. A violation of this balance of mucus production and clearance may lead to many clinical problems. Mucus hypersecretion is a common feature in CRS. Heung-Man et al. examined expression of MUC8 messenger RNA (mRNA) and protein in mucosae of patients with CRS and control subjects and found an increased synthesis of MUC8 mRNA and protein in the CRS specimens than in the normal sinus mucosae.

Immunocompromised state

Dysfunction of the immune system may occur during the life and present in CRS. T-lymphocytes showed abnormal proliferation in response to antigen recall. Low immunoglobulin (Ig) G, A and M titres were found in 18, 17 and 5% of the patients with refractory sinusitis, respectively. The most common immune deficiency associated with CRS is an IgG subclass deficiency. It was found that CRS was present in more than half of HIV-positive population.

Environmental and other non-host factors

Substantial evidences support the premise that environmental and other non-host-related factors, such as air pollution, smoke, allergens, viruses, fungi and bacteria, predispose individuals to CRS.

Air pollution

Cigarette smoking was associated with a higher prevalence of CRS. In spite of in vitro data of the toxic effects of pollutants on respiratory epithelium, there is no convincing evidence of the etiologic role of toxins such as ozone in CRS.

Aspirin intolerance

Samter’s triad is a combination of CRS with nasal polyps, asthma and aspirin sensitivity. It is though that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of the enzyme cyclooxygenase-1 (COX-1) in the arachidonic acid metabolism pathway, resulting in an increase in the activity of the enzyme 5-lipoxygenase in the affected patients. The products of the 5-lipoxygenase pathway include the leukotrienes (LTC4, LTD4 and LTE4), which are potent inflammatory mediators that can induce mucus secretion, bronchoconstriction of the airway, and edema of the nasal mucosa and attract eosinophils into the airway. Aspirin intolerant patients show elevated basal levels of leukotrienes and reduced basal levels of prostaglandin E2. Patients with Samter’s triad generally tend to have more severe symptoms of CRS with nasal polyposis and asthma than do patients without the triad. Nasal polyposis was found in the majority of cases, often recurrent after previous surgery.

Allergy and asthma

Review articles on CRS have suggested that atopy predisposes to its development, tempting to speculate that allergic inflammation in the nose predisposes the atopic individual to the development of CRS. It has been postulated that swelling of the nasal mucosa in allergic rhinitis at the site of the sinus ostia may compromise ventilation and even obstruct them, leading to mucus retention and infection. Numerous of studies report that markers of atopy are more prevalent in population with CRS. However, the role of allergy in CRS is questioned by other epidemiologic studies showing no increase in the incidence of infectious rhinosinusitis during the pollen season in pollen sensitized patients.

The association between asthma and CRS has long been established. In general, CRS in patients with asthma tends to be more severe and refractory to conventional medical management than it is in patients without asthma. Multiple theories have been proposed to explain the association between asthma and CRS. According to an early theory, sinus...
material is aspirated into the lower airways, where it irritates the epithelium and exacerbates asthma. According to another theory, which involves a proposed sinonasal-bronchial reflex, the bronchoconstriction that asthmatic patients experience is caused by CRS-induced vagal stimulation. Support for this mechanism is provided by the fact that many patients with asthma report an increase in asthma symptoms during acute episodes of CRS. In patients with both asthma and CRS, respiratory epithelial cells produce a range of cytokines (interleukins: IL-3, IL-4, IL-5, IL-13, eotaxin and granulocyte-macrophage colony-stimulating factor) that could affect the recruitment and activation of inflammatory leukocytes. The resultant increase in inflammatory mediators (histamine, thromboxane and leukotrienes) leads to the increased vascular permeability, mucus hypersecretion, ciliary impairment and mucosal edema, which can obstruct the sinus ostia and create an optimal environment for bacterial overgrowth.

**Fungal infection**

The role of fungi in the causation of CRS is still controversial. The rate of fungal infection in the nasal passage by culture, histopathology, or polymerase chain reaction (PCR) is reported to be in the range of 26.7–93% in CRS. Allergic fungal rhinosinusitis (AFR) is a noninvasive IgE-mediated form, accounting for 5–10% of all CRS cases, by conventional criteria. By the Mayo Clinic criteria, chronic eosinophilic rhinosinusitis is present in nearly 100% of patients with rhinosinusitis or nasal polyps. The clinical features of AFR include refractory sinusitis, presence of eosinophils and allergen-specific Th2 cells in allergic mucin, and the absence of any kind of invasive fungal involvement in the tissues. Fungal rhinosinusitis tends to affect a relatively young population of individuals who are generally atopic and recognized as asthmatic. Six steps were found in the pathogenesis of AFR: the host becomes sensitized to fungal antigens; fungal spores become trapped in nasal or sinus mucus and germinate into viable hyphae; in seasonal and perennial allergic rhinitis, the profile of T-cell cytokines in nasal tissue fits the classic Th2 profile, with the production of cytokines IL-5, IL-13, and granulocyte-macrophage colony-stimulating factor that depend on the bone marrow. Some studies have shown that nasal polyps contain increased numbers of IL-5-producing T-lymphocytes and CD34+ eosinophil precursor cells; damage occurs to the mucosa, facilitating bacterial penetration of the mucosa that leads to bacterial infection and further perpetuates an inflammatory process.

**Bacterial infection**

Although CRS is not necessarily an infectious condition, bacteria are often found within the ethmoid and maxillary sinuses. The most common were coagulase-negative staphylococci (31–56% of isolates), Hemophilus influenzae (25%), Staphylococcus aureus (20–39%), Streptococcus pneumoniae (9–17%). Although it is often hypothesized that CRS evolves from acute rhinosinusitis, this has never been proven. Furthermore, the role of bacteria in CRS is far from clear. The presence of intracellular Staphylococcus aureus in epithelial cells of the nasal and sinus mucosa has been suggested to pay a significant risk factor for recurrent episodes of rhinosinusitis due to persistent bacterial clones, which appear to be refractory to antimicrobial and surgical therapy. A recent prospective study revealed that colonization of the middle meatus with Staphylococcus aureus is significantly more frequent in CRS with nasal polyposis (60.3%), compared to CRS without nasal polyposis (27.3%). Staphylococcus aureus enterotoxins (SAEs) are able to induce more severe eosinophilic inflammation as well as the synthesis of a multiclonal IgE response with high total IgE concentrations in the tissue, which would suggest that SAEs are at least modifiers of disease in CRS with nasal polyps. Min et al. have shown that SAEs have a ciliostatic effect on the sinus mucosa. Histopathologic findings, induced by SAEs, included severe submucosal edema, epithelial disruption, and inflammatory cells infiltration (predominantly neutrophils).

**Helicobacter pylori and laryngopharyngeal reflux**

Helicobacter pylori DNA has been detected in between 11 and 33% of sinus samples from the patients with CRS, but not from the controls. However, this does not prove a causal relationship.

**Conclusions**

Chronic rhinosinusitis is a multifactorial problem involving numerous host and non-host factors. The roles of factors such as allergy, fungal infection and bacterial enterotoxins warrant further study. It is clear that these factors must be taken into account in the diagnosis and long-term management of CRS.

**References**


