Chronic Rhinosinusitis Phenotypes: An Approach to Better Medical Care for Chronic Rhinosinusitis

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The review articles in *The Journal of Allergy and Clinical Immunology: In Practice* focus on phenotypes of chronic rhinosinusitis (CRS), one of the most common diseases in the United States and other countries of the world. How did interest in CRS phenotypes come about? First, the senior author, Richard F. Lockey, MD, has always believed that CRS is primarily a medical disease, one that necessitates a complete history and physical examination to identify the comorbid and preexisting conditions that are related to or predispose to this disease. Second, just as asthma is not one disease, so too, CRS is not one disease. Identifying phenotypes will lead to a more appropriate diagnosis and treatment regimen. Third, the availability of rhinolaryngoscopy, a simple and vital modern-day diagnostic tool, enables any physician, regardless of the specialty, to confirm and treat this disease. The editorial leadership of *The Journal of Allergy and Clinical Immunology: In Practice* agreed with this concept, and Dr Lockey elicited the collaboration of Dr Seong Cho, a University of South Florida fellow faculty member, and Dr Claus Bachert, both of whom are clinicians who do CRS basic research. The definitions of CRS phenotypes will precede the definitions of various CRS endotypes. Both concepts will lead to better care of patients with this chronic disease.

An estimated prevalence of CRS is 5% to 15% of the adult population[1-5] and costs the health care system in the United States approximately $8 billion per year.[6] CRS also significantly affects the quality of life in some symptom domains even more so than do other chronic diseases, such as angina and back pain.[7] However, there is a tremendous gap between scientific evidence, that is, the lack of good quality CRS clinical and translational studies versus clinical practice. Stepwise approaches for the diagnosis and treatment of CRS, similar to guidelines for asthma, have not been validated and need to be established. The European position paper on rhinosinusitis and nasal polyps guidelines show stepwise approaches according to the severity of disease, but these have not been validated.[8] Much of the lack of knowledge about CRS leads to a misconception by most physicians that CRS is primarily a surgical versus a medical disease. This editorial outlines the authors' approach to CRS using the information obtained from the literature and the international experts in this series of articles that define various CRS phenotypes.

DEFINITION OF CRS

What is CRS? One definition of CRS is that it is an inflammatory condition of the nose and paranasal sinuses persisting for at least 12 weeks characterized by 2 or more nasal/sinus symptoms, one of which includes nasal obstruction or nasal discharge ± facial pressure/pain and ± reduced smell.[8] In addition, endoscopic signs of mucopurulent discharge or edematous/mucosal obstruction of the middle meatus or radiologic abnormalities, such as mucosal changes within the ostiomeatal complex or sinuses, support the diagnosis. As the definition indicates, CRS is a chronic inflammatory disease of the mucosal membranes of the upper airway just as are asthma and chronic obstructive pulmonary disease, chronic inflammatory diseases of the lower airway. The definition itself as well as the clinical presentation of CRS indicates that it is primarily a medical problem. Defining CRS phenotypes is a critical step in determining optimal medical or surgical treatment.

DIFFERENTIAL DIAGNOSIS AND COMORBID/COEXISTING CONDITIONS

A detailed history and physical examination is the ideal approach for any patient with any disease, and in this case, so too with CRS. It should include all the presenting symptoms and signs associated with CRS. Some of these include discolored nasal discharge from the nares or into the posterior pharynx, facial discomfort, pain in the maxilla, foul smell or taste, rhinorrhea, postnasal drip, nasal stuffiness, lethargy, fatigue, and others. Likewise, coexisting and comorbid conditions or diseases, which present with some of the same symptoms of CRS, must be addressed. An example of the latter is a patient referred for "sinus headaches." However, the etiology of these headaches may be temporomandibular joint dysfunction, tension headaches, or secondary to a neurologic problem, not CRS. Allergic and nonallergic rhinitis can predispose to CRS and must be considered as a confounding problem in evaluating patients with this

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TABLE I. CRS phenotypes

1. CRSsNP
2. CRSwNP
3. CRS with aspirin-exacerbated respiratory disease
4. Allergic fungal sinusitis
5. Infectious CRS
6. CRS with cystic fibrosis
7. Other CRS phenotypes
a. CRS with immune deficiencies such as common variable immunodeficiency and specific antibody deficiency
b. CRS with immotile cilia syndrome
c. CRS with anatomical abnormalities
d. Biomarker based (endotypes)
1) Eosinophilic CRS vs noneosinophilic CRS
2) Allergic CRS vs nonallergic CRS
3) T_H2 high vs T_H2 low
4) High IgE vs normal IgE

disease. Laryngopharyngeal reflux disease/gastroesophageal reflux disease can also predispose or occur concomitantly with CRS. A globus sensation associated with laryngopharyngeal reflux disease/gastroesophageal reflux disease can often be confused with some of the presenting symptoms of CRS, that is, laryngopharynx clearing ("throat clearing") and "postnasal drip." Certain medical conditions also predispose to CRS, often times overlooked by clinicians. Some of these include primary and secondary immunodeficiency diseases, cystic fibrosis, mucociliary dysfunction, drug abuse, and various types of rhinitis.

IDENTIFICATION OF CRS PHENOTYPES

The identification of a given CRS phenotype (Table I) is primarily based on the clinical evaluation; for example, does the patient have chronic rhinosinusitis with nasal polyps (NPs) (CRSwNP) or chronic rhinosinusitis without nasal polyps (CRSsNP)? If they have polyps, do nonsteroidal inflammatory drugs exacerbate their respiratory disease? Is their CRS infectious? If so, is it associated with underlying medical problems? Is the etiology fungal in origin? Likewise, some CRS is associated with anatomic abnormalities or congenital diseases such as immotile cilia syndrome and cystic fibrosis. In addition to phenotyping CRS, endotyping CRS with various biomarkers should become more possible in the future as endotypes are better defined, that is, eosinophilic versus neutrophilic CRS.

Essential to phenotyping CRS is rhinolaryngoscopy. A competent rhinoscopic examination is essential to diagnose the CRS phenotype. Anterior rhinoscopy (via the anterior nares) visualizes at best only the first one-third of the nasal cavity and is inadequate to visualize the posterior naso-oral or laryngeal pharynx. Rhinolaryngoscopy is a simple and inexpensive procedure and should be performed routinely in patients suspected of any persistent upper airway problem, in particular, CRS. Just as office spirometry is a routine procedure to assist in the diagnosis of asthma, so too should rhinolaryngoscopy be used on a regular basis for CRS.

Other confirmatory diagnostic tools to help phenotype CRS can include *in vivo* and *in vitro* IgE tests, an aspirin challenge to rule in or rule out aspirin-exacerbated respiratory disease, and a screening immunologic evaluation, in particular, immunoglobulin levels and specific antibody titers. In addition, a sweat chloride and a nasomucosal biopsy may be indicated. Patients refractory to therapy may need an additional evaluation to define the underlying pathophysiological mechanisms causing the disease. For example, a long-term macrolide antibiotic treatment for patients with CRSsNP can be more effective in those who have normal IgE versus abnormal IgE levels.[9] Defining whether the inflammation is eosinophilic versus neutrophilic can also predict prognosis and help guide a treatment plan. For example, there is a significant age-related decline in eosinophilic inflammation with an increased prevalence of NPs and comorbid asthma in subjects with CRS as reported in a US cohort.[10] Another example is that elderly versus nonelderly Asian subjects with noneosinophilic NPs had better endoscopic scores at 12 months following surgery.[11] As previously indicated, endotyping airway diseases are just now becoming a reality. This is illustrated by the number of biologics available or now under investigation to treat severe asthma. The same biologics have been used in small clinical trials in patients with CRSwNP with efficacy. The topic of endotyping and biologics is discussed below.

OPTIMAL USE OF IMAGING STUDIES

A computed tomography (CT) scan can be vital to diagnose or treat CRS. However, the overuse or misuse of imaging techniques is a major problem in modern medicine. A CT scan of the sinuses should be obtained primarily when rhinolaryngoscopy indicates structural abnormalities as a suspected cause of CRS or other complications from CRS are suspected. Structural abnormalities, such as concha bullosa, Haller cell, and paradoxical middle turbinate abnormalities, usually do not cause CRS. If they did, CRS theoretically would be more common in younger individuals because these structural abnormalities are present since childhood. A CT also is most useful when adequate and prolonged medical therapy has failed and surgery is contemplated. A *New England Journal of Medicine* article discusses an increasing concern for the overuse of CT scans as an important source of radiation exposure and increased cancer risk.[12] It concludes that there is direct evidence from epidemiologic studies that the organ doses from 2 or 3 CT scans result in radiation doses in the range of 30 to 90 mSv. This may result in an increased risk of cancer for both adults and children. The authors have seen children who have had 2 or 3 CT scans of their head in the first 5 years of life in the process of evaluating them for CRS, CRS surgery, and postoperative follow-up. Likewise, the authors are concerned that surgery for CRS has become so much more common for children than it was even 20 years ago, when almost all children with chronic sinusitis were treated medically. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines indicate that surgery of the sinuses is rarely indicated for children, with the exception of CRS in patients with cystic fibrosis.[8] Additional concern is that CT scans, when they are obtained, are frequently overinterpreted by radiologists and physicians. For example, a CT scan report often states "Mucosal thickening in the right and left maxillary sinuses compatible with sinusitis." This automatically triggers the physician to think that the patient has "CRS," not knowing that a common cold, allergic rhinitis, and just plain mucosal cysts or membrane scarring can account for these changes. This overinterpretation leads to excessive treatment for some individuals who do not have other symptoms and signs of CRS and only have a CT scan with so-called mucosal thickening.