Lipid Mediators in Aspirin-Exacerbated Respiratory Disease

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KEYWORDS

• AA (arachidonic acid) • AERD (aspirin-exacerbated respiratory disease) • Asthma
• COX (cyclooxygenase) • Leukotriene • 5-LO (5-lipoxygenase)
• NSAID (nonsteroidal inflammatory drug) • Prostaglandin

KEY POINTS

- Patients with aspirin-exacerbated respiratory disease (AERD) have an anomalous underlying chronic inflammation characterized by mast cell and eosinophil infiltration/activation in the respiratory tract that is further exacerbated by nonsteroidal inflammatory drug (NSAID) ingestion.
- Dysregulation of arachidonic acid metabolism, both of the cyclooxygenase and 5-lipoxygenase pathways, is key to AERD pathogenesis.
- NSAID blockade of the bronchoprotective and antiinflammatory prostaglandin (PG) E_2 and resulting excessive production of the bronchoconstrictive and proinflammatory lipid mediators PGD_2 and cysteinyl leukotrienes C_4, D_4, and E_4 create a proallergic milieu in the airways of asthmatics with AERD.

INTRODUCTION

History

Aspirin-exacerbated respiratory disease (AERD) is a chronic inflammatory disorder of the respiratory tract characterized by the tetrad of asthma, nasal polyposis, rhinosinusitis, and acute exacerbations of the asthma and rhinosinusitis on ingestion of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs). Although reactions associated with the use of aspirin were described as early as 1902 by Hirschberg[1], just a few years after its synthesis, the entity of AERD was not described until 1922 by Widal and colleagues.[2] The clinical phenomenon of AERD was further delineated by Samter and Beers[3] in 1968 after they published a series of patients with asthma, nasal polyps,

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Immunol Allergy Clin N Am 36 (2016) 749–763
http://dx.doi.org/10.1016/j.iac.2016.06.009 **immunology.theclinics.com**
0889-8561/16/$ – see front matter

and aspirin sensitivity, and the entity became known as the Samter triad. The addition of chronic rhinosinusitis has since been recognized as a part of the clinical entity.[4] The disease has taken on several names in addition to Samter triad, including aspirin-induced asthma, aspirin-intolerant asthma, triad asthma, and aspirin hypersensitivity. There is now a preference for AERD because this is a more encompassing and accurate name; it indicates that this is an underlying respiratory tract disease that is exacerbated but not caused by NSAIDs. In 1971, Vane[5] published his discovery of the mechanism of action of aspirin, and, soon after, the capability of aspirin to inhibit the cyclooxygenase (COX) enzyme was implicated in the underlying pathogenesis of AERD, suggesting a dysregulation of arachidonic acid (AA) metabolism.[5,6] Although significant advancements in the understanding of the pathogenesis of AERD have been achieved since that time, in particular the skewing of the AA metabolic pathway to the overproduction of the 5-lipoxygenase (5-LO) products, the leukotriene (LT)s, much remains unknown about this disease of the upper and lower respiratory tract.

Prevalence

The prevalence of AERD has been poorly understood because it is not always distinguished from other forms of asthma in the population. A recent meta-analysis of AERD prevalence among asthmatics examined 27 studies deemed appropriate out of 1770 articles on this topic and found a prevalence ranging from 5.5% to 12.4% with an estimated prevalence of 7.2% among all studies.[7] Patients with severe asthma had the highest prevalence of AERD at 14.9%, followed by patients with nasal polyps (9.7%) and chronic rhinosinusitis (8.7%).[7]

Clinical Presentation

The disease typically presents in the second to fourth decade with chronic rhinitis and hyposmia.[8] The usual progression is subsequent development of sinusitis and nasal polyposis with a prominent eosinophilic infiltrate within months, and then symptoms typical of asthma within 1 to 2 years. Classically, such patients are sensitive to NSAIDs from the beginning of the manifestation of disease, and experience an exacerbation of symptoms with NSAID use in a dose-dependent fashion. Symptoms occur between 30 minutes to 3 hours after ingestion and can range from rhinitis to life-threatening bronchospasm. However, NSAID sensitivity may be noticed at any point in the disease depending on patient use of these medications. Although this is the classic presentation, atypical presentations are reported as well; most notably examples of patients with asthma who have tolerated NSAIDs in the past but become sensitive only later in the disease process.

Pathophysiology

The cause of AERD is not known and the pathophysiology is only partially understood. Knowledge of the disease mechanism comes predominantly from observations showing differences that have been identified in individuals with AERD compared with aspirin-tolerant asthmatic individuals as well as nonasthmatics. From the time of disease onset, patients with AERD develop upper respiratory inflammation manifested as chronic rhinosinusitis with polyposis that progressively involves the lower respiratory tract in the form of persistent asthma. Although patients with AERD do have reactions after exposure to NSAIDs, with acute increases in inflammatory mediators after aspirin challenge, they also have baseline increases in airway inflammation compared with aspirin-tolerant controls.[9] Histologic evaluation has shown an increased density of eosinophils in the bronchial mucosa and submucosa as well as within the nasal mucosa and epithelium at baseline in biopsies