Aspirin-Exacerbated Asthma: Avoiding Challenge Is Still Challenging

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The term ‘aspirin-exacerbated respiratory disease’ (AERD), instead of the formerly used ‘aspirin-induced asthma’, highlights that the core issue for these patients is not drug hypersensitivity, but the underlying chronic inflammatory respiratory disease, occasionally exacerbated by aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) [1].

The gold standard for diagnosing AERD is aspirin challenge, which may be performed through three different routes of provocation challenges: oral, bronchial and nasal inhalation, the oral challenge being considered the test with the best sensitivity and specificity [2].

As well as being time-consuming, aspirin challenges are not without risk, and more than a third of patients have been reported to experience late reactions following bronchial aspirin challenge [3]. For these reasons, in vitro tests would be welcome, but unfortunately, till now, none could be recommended for routine diagnosis [4]. More recently, three in vitro tests measuring aspirin/NSAID-specific peripheral blood leukocyte activation have been proposed: measurement of sulfidoleukotriene release with inconsistent results [5, 6], measurement of cell surface molecule CD63 expression upon in vitro challenge [7] with quite variable specificity and sensitivity and measurement of aspirin-triggered 15-HETE generation, which appears to be promising [8]. Its clinical usefulness has, however, not yet been confirmed by larger studies.

AERD is an organ-specific disease, characterized by abnormalities in the biosynthesis of eicosanoid mediators and eicosanoid receptor expression. The biochemical hallmark of AERD is enhanced cysteinyl leukotriene (CysLT) production both at baseline [9, 10] and following aspirin challenge [11, 12].

As AERD is not a systemic disease, it is not surprising that studies of different inflammatory cells in the blood have so far failed to produce consistent support for specific NSAID-induced ex vivo activation of cells from subjects with AERD. Higashi et al. [13], in this issue, reason that acetylsalicylic acid intolerance might be maintained in sputum cells when they are recovered from the lower airways of patients with asthma, if these cells were challenged by aspirin ex vivo. They found that release of CysLTs by sputum cells from patients with AERD was neither induced by aspirin ex vivo when cells were collected at baseline nor in sputum cells recovered after lysine-aspirin-induced bronchoconstriction. On the other hand, they found that the release of CysLTs from sputum cells triggered by ionophores in both instances was higher in the AERD group, both at baseline and after the lysine-aspirin bronchoprovocation. Their results confirm that AERD is characterized by enhanced CysLTs production both at baseline and following aspirin challenge. The difference in the amounts of CysLT release between aspirin-sensitive and aspirin-tolerant asthmatic patients ap-
peared related to the number of eosinophils. AERD is actually an eosinophilic phenotype of asthma and chronic rhinosinusitis.

The inability to demonstrate intolerance to NSAIDs in blood cells as well as in sputum cells strongly points to the role of airway resident cells in the adverse reaction.

Two cells appear to be the best candidates to explain acute asthma exacerbation following aspirin challenge: airway epithelial cells and bronchial mast cells, neither of which is represented in peripheral blood or in sputum cells.

Downregulation of COX-1 has been shown in the airway epithelial cells of patients with AERD; this may result in a further decrease of prostaglandin E$_2$ (PGE$_2$) production upon NSAIDs administration [14]. There is evidence that PGE$_2$ ameliorates aspirin-induced disease, at least partly, by inhibiting excessive CysLTs synthesis [5, 15]. Mast cells are a major source of the release of the autacoid mediators histamine, prostaglandin D$_2$ (PGD$_2$) and leukotriene C$_4$ (LTC$_4$) [16], all of which are potent contractile agonists of airway smooth muscle. In vivo studies suggest that mast cells are directly activated by aspirin in AERD. Aspirin-sensitive patients have raised levels of the PGD$_2$ metabolite (9α,11β-PGF2) and tryptase in their blood prior to exposure to aspirin. In most patients, following challenge, these levels rise still further [17]. After segmental lysine aspirin challenge a trend in patients towards an increased histamine release with no inhibition of PGD$_2$ production has been shown [11]. Conversely, in mast cells cultured from peripheral blood progenitors in aspirin-sensitive patients, neither baseline nor IgE-induced release of histamine or CysLTs was upregulated when the cells were incubated with aspirin [18]. Overall, these findings suggest that chronic ongoing mast cell activation is a feature of AERD at baseline, and this may be aggravated further as a result of aspirin provocation. However, a mechanism for direct mast cell activation by aspirin is unclear. A possible explanation may reside in the cross talk between airway epithelial cells and bronchial mast cells. At baseline, as a result of an unknown injury (bacterial?), airway epithelial cells produce tissue cytokines (i.e. thymic stromal lymphopoietin) [19] which drive Th2 inflammation, characterized by heavy eosinophil and mast cell infiltration of bronchial mucosa [20]. These cells may be the source of leukotrienes and PGD$_2$, which have been reported to increase at baseline and after aspirin challenge in a wide variety of biological samples of patients with AERD. Moreover, mast cells secrete the pro-inflammatory cytokines interleukin IL-4, which upregulates both the pathway responsible for CysLTs synthesis and the expression of CysLT receptors [21, 22], IL-13, which selectively downregulates PGE2 biosynthesis while upregulating the PGE2-metabolizing enzyme 15-prostaglandin dehydrogenase in human airway epithelial cells [23] and IL-5, which plays a major role in recruitment and survival of eosinophils. Eosinophils, in turn, are a major source of the same cytokines, so that they may contribute to amplify and maintain airway inflammation.

As not all patients with Th2-driven asthma develop AERD, inherited susceptibility may probably play a role [24].

In conclusion, although AERD is a relatively common phenotype of asthma, affecting primarily adults but also children with physician-diagnosed asthma, it is often unrecognized and underdiagnosed. Unfortunately, there is no simple in vitro test to diagnose AERD and in vivo aspirin challenge still remains the gold standard. Ex vivo stimulation of sputum cells nevertheless appears a promising method to assess capacity for CysLT production in the airways of subjects with asthma. It would be useful to evaluate novel therapeutic approaches targeting aspirin-sensitive patients.

References


