



Upper airways in aspirin-exacerbated respiratory disease

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Purpose of review

This review updates the status of chronic rhinosinusitis with nasal polyps (CRSwNP) in aspirin-exacerbated respiratory disease (AERD) in the contexts of epidemiology, diagnosis, pathogenesis, and treatment.

Recent findings

Recent studies have shown that prostaglandin E₂ (PGE₂) deficiency induces an AERD phenotype in PGE₂ synthase-1 knock-out mice and also PGE₂ resistance in granulocytes of AERD patients. The numbers of platelet-adherent leukocytes increase in AERD patients, enhancing production of cysteinyl leukotrienes (CysLTs) via transcellular metabolism of arachidonate. INF- γ released from eosinophils of the sinus tissue of AERD patients promotes eosinophil maturation, increases leukotriene-associated gene expression, and releases CysLTs. The serum periostin level has been suggested to be a useful biomarker predicting the AERD/CRSwNP phenotype. Aspirin desensitization was reported to decrease the levels of CD4⁺ T cell-derived cytokines, including INF- γ and IL-10, in line with the newly defined role of INF- γ in AERD.

Summary

Recent findings further support the notion that arachidonic acid metabolism is dysregulated in AERD patients. This is reflected by resistance to PGE₂, overproduction of CysLTs by enhanced numbers of platelet-adherent leukocytes, and cellular stimulation by INF- γ released from eosinophils. Aspirin desensitization may be a useful treatment option in AERD patients exhibiting recalcitrant CRSwNP.

Keywords

aspirin hypersensitivity, asthma, chronic rhinosinusitis, desensitization, nasal polyp

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is characterized by hypersensitivity to aspirin and nonselective inhibitors of cyclooxygenase (COX), asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP) [1]. Explorations of the natural course of AERD have revealed that CRSwNP triggered by viral infection-associated rhinitis is an established feature of AERD [2]. Aspirin hypersensitivity in patients with CRSwNP is associated with a particularly severe, persistent, and refractory form of the disease [2]. In addition, the upper and lower airways of those diagnosed with AERD share similar pathogenic manifestations, including intense eosinophilic infiltration and dysregulation of arachidonic acid metabolism [3]. Local and/or systemic immune response(s) to staphylococcal enterotoxins have/has also been implicated in the pathogenesis of CRSwNP in AERD patients [3]. Aspirin desensitization has been suggested as a useful treatment for refractory CRSwNP in AERD patients, although possible means toward this end have not been fully

described [1,4[¶]]. Herein, we review the upper airway status of AERD patients, highlighting recent advances in our understanding of CRSwNP in such patients.

EPIDEMIOLOGY AND CLINICAL FEATURES

AERD occurs in about 0.3–0.9% of general populations, affects 10–20% of asthmatic patients, and is present in about 8–26% of those diagnosed with CRSwNP [5]. Symptom onset is both earlier and more severe in females than males [2,6]. Sex

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KEY POINTS

- CRSwNP is the most common comorbid condition associated with AERD. CRSwNP is characterized by intense eosinophilic infiltration, emphasizing the need for more aggressive medical and surgical interventions.
- Dysregulation of arachidonic acid metabolism is a major cause of CRSwNP in AERD patients. PGE₂ levels are reduced via inhibition of the COX pathway by aspirin and other nonselective COX inhibitors, and CysLTs are overproduced upon activation of the 5-lipoxygenase pathway.
- Aspirin desensitization is recommended for CRSwNP patients with AERD who are refractory to medical and surgical treatments. Biologicals including anti-IgE and anti-IL-5 antibodies are future therapeutic options.

hormones may influence both autoimmune responses and repair mechanisms and may explain the observed gender bias [6]. AERD is common in middle-aged females and usually presents with symptoms of severe chronic rhinosinusitis and asthma [2,3]. Patients exhibit variable clinical manifestations, ranging from rhinitis, to nasal polyps, to asthma. However, as not all patients develop asthma, the term 'AERD' is to be preferred to 'aspirin-intolerant asthma' [7]. The most common comorbid condition of the upper airway in AERD patients is CRSwNP [3,7]. The first clinical symptom of AERD of the upper airway is usually nasal congestion and appears during the third decade of life, associated with hyposmia and chronic rhinorrhea; the disease progresses to chronic pansinusitis followed by development of nasal polyps that regrow both frequently and rapidly despite repeated surgery [5]. Other symptoms include facial pressure, a post-nasal drip, nasal discharge, purulence, anosmia, a chronic cough, headache, dental pain, ear pressure, fatigue with sleep deprivation, and halitosis [5,7].

CRSwNP in AERD patients has an aggressive course. The nasal cavity becomes filled, and the polyps protrude anteriorly into the face or posteriorly into the nasopharynx [5]. CRSwNP tissue exhibits an edematous and generally eosinophilic mucosa [3]. The most significant pathological finding of CRSwNP in AERD patients is infiltration and activation of eosinophils, associated with release of the contents of eosinophil granules, including eosinophil cationic protein (ECP) and/or major basic protein [3,7].

ALTERATIONS IN ARACHIDONIC ACID METABOLISM

Cysteinyl leukotrienes (CysLTs) are potent pro-inflammatory mediators in the context of airway

inflammation and can induce bronchoconstriction, eosinophilic inflammation, mucus hypersecretion, and increases in vascular permeability [8[•]]. Significant increases in CysLT levels have been noted in CRSwNP sinonasal tissues of AERD patients, compared with aspirin-tolerant asthma (ATA) patients [9]. Moreover, remarkable reductions in urinary leukotriene (LT) C₄ levels have been reported after endoscopic sinus surgery to treat CRSwNP in AERD patients [10]; this may be a consequence of debulking of sinus CysLT-producing cells. Enhanced production of CysLTs in CRSwNP tissue is associated with elevated expression of LTC₄ synthase, the rate-limiting enzyme in CysLT biosynthesis [11]. Higher level expression of CysLT receptors, including both CysLT receptor 1 (CysLTR1) and CysLTR2, was also evident in the CRSwNP mucosal tissue of AERD patients, compared with those with ATA [11–13].

PGE₂ exerts both an anti-inflammatory effect and a bronchoprotective role, and its anti-inflammatory effects are induced via stimulation of the E-prostanoid (EP)₂ receptor [14]. Reduced PGE₂ production and downregulation of COX-2 and the EP₂ receptor were evident in the nasal polyp (NP) tissues of CRSwNP in AERD patients, compared with ATA patients [9,15]. Recently, Liu *et al.* [16^{••}] showed that mice selectively lacking microsomal PGE₂ synthase-1 (mPGES-1) developed an AERD-like phenotype in response to aspirin, featuring airflow obstruction, production of CysLTs, and lung mast cell activation. Also, *Dermatophagoides farinae*-treated mice lacking EP₂ receptors developed a partial aspirin-sensitive phenotype. Furthermore, the cited authors also showed that granulocytes in the peripheral blood of AERD patients exhibited minimal suppression of LT generation when exposed to PGE₂ and EP receptor-selective agonists, although the EP receptor expression levels were normal [17^{••}]. Altogether, the data suggest that reduced PGE₂ production, or development of resistance to the anti-inflammatory effect of PGE₂, may play key role(s) in the pathogenesis of upper airway disease in AERD patients, as do overproduction of CysLTs and increased expression of CysLTR1 and CysLTR2.

INFLAMMATORY CELLS AND CYTOKINES

A strong eosinophilic infiltration is a key histological feature of CRSwNP in AERD patients, compared with those with other types of NPs [3]. AERD patients exhibit increased levels of inflammatory mediators including CysLTs, ECP, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), eotaxin, and regulated on activation, normal T cell expressed and secreted (RANTES); all are produced predominantly by eosinophils [3,9,18]. Steinke *et al.* [19^{••}] recently showed that higher INF-γ levels produced

by eosinophils in NP tissue distinguished AERD from chronic hyperplastic eosinophilic sinusitis. The cited authors found that INF- γ promoted maturation of eosinophil progenitors, increased the levels of eosinophil-associated gene expression (including that of the CysLTR1, P2Y12, and LTC₄ synthase), and increased secretion of CysLTs from activated eosinophils [19[■]]. It was also shown that eosinophils differentiated in the presence of interferon (IFN)- γ exhibited robust secretion of both eosinophil-derived neurotoxin and CysLTs, upon activation with aspirin (and even ketorolac, a non-selective COX inhibitor) [20[■]]. Mast cells can be directly activated by aspirin [20[■]], and play a role in AERD via release of histamine and tryptase, and by synthesizing CysLTs and PGD₂ [3,5]. Increased levels of platelet-adherent granulocytes (mostly eosinophils) have been noted in NP tissues of AERD patients, associated with overproduction of CysLTs and thromboxane A₂ via transcellular metabolism of eicosanoids [21]. These data suggest that platelets play a major role in AERD pathogenesis.

STAPHYLOCOCCAL ENTEROTOXINS

Local or systemic immunological responses to staphylococcal enterotoxins play important roles in the pathogenesis of CRSwNP [22]. The levels of specific IgEs to staphylococcal enterotoxins in NP tissue of AERD patients are significantly higher than those in normal mucosa [23] or in ATA patients [24,25], correlating with the levels of ECP and IL-5. This indicates that local IgE responses to staphylococcal enterotoxins may drive eosinophilic activation in the NP tissues of AERD patients [24,25]. Staphylococcal enterotoxins (acting as superantigens) have been shown to activate Th2 cells and trigger release of Th2 cytokines, including IL-4, IL-5, and IL-13. These events trigger the development of eosinophilic inflammation, a characteristic of CRSwNP [26]. Recently, the presence of serum-specific IgE to staphylococcal enterotoxins has been reported to suggest a high risk of development of bronchial asthma, independently of the presence of specific IgEs binding to common inhalant allergens. The data imply that production of polyclonal IgEs against staphylococcal enterotoxins may play a role in development of airway inflammation [27]. Thus, staphylococcal enterotoxins contribute to eosinophilic activation in CRSwNP tissues of AERD patients via polyclonal activation of T and B cells, with induction of Th2 cytokines and the synthesis of polyclonal IgEs targeting staphylococcal enterotoxins.

DIAGNOSIS

Patients with histories of asthmatic attacks after ingestion of aspirin or other nonselective COX

inhibitors, or those with chronic rhinosinusitis, nasal polyps, and/or asthma, should be suspected of having AERD. Some patients have definite histories of adverse reactions to nonselective COX inhibitors and these afford clues to the presence of AERD. CRSwNP is a specific characteristic of the upper airway of AERD patients [3,5]. Definitive in-vitro tests diagnosing AERD are not available, and the gold standard test is aspirin challenge, which is indicated in patients with asthma and CRSwNP [28]. Four routes of challenge may be used; these are the oral, bronchial inhalation, nasal inhalation, and intravenous routes [1,28,29[■]]. The oral challenge test, using the Stevenson protocol, is usually administered in the USA [1]. The aspirin dose is increased every 2–3 h over 3 days beginning with 30 mg and advancing to a cumulative dose of 1000 mg; the forced expiratory volume in 1 second (FEV₁) is measured every hour during challenge [1,28]. The baseline FEV₁ should be at least 1.5 l and over 70% of the predicted value [1,28]. The bronchial challenge test is safer and quicker than the oral challenge test [28]. The nasal aspirin challenge test is recommended for patients with contraindications to use of the oral or inhalation tests [28,29[■]]. Although the nasal challenge test is safe when used to diagnose AERD (because systemic symptoms or bronchospasm rarely develop [28]), the sensitivity and negative predictive value are lower than those of the other two tests [28,29[■]]. An intravenous provocation test using NSAIDs may also be employed [28]. Careful history taking of patients with asthma and rhinosinusitis is very helpful. The probability of a positive oral aspirin challenge test is over 80% in those with a history of a single reaction to NSAIDs, and increases to 90% if two such reactions are reported [6].

Along with provocation tests, imaging studies such as an ostio-meatal unit computed tomography (CT) scan and a paranasal sinuses series may be useful to determine or confirm the presence of disease and to assess the severity of CRSwNP [30]. A CT scan or a plain X-ray reveals opacification of both sinuses in most AERD patients. Other diagnostic procedures including rhinoscopy and nasal endoscopy may be helpful to diagnose CRSwNP [3]. Acoustic rhinomanometry can be used to measure nasal obstruction [5].

No adequately sensitive and specific in-vitro test is available for diagnosis of AERD. Although many genetic variations have been reported to serve as potential markers of the AERD or CRSwNP phenotype, it has been suggested that HLA DPB1*0301 reliable genetic marker of CRSwNP in AERD patients, as patients carrying this allele exhibited a significantly higher prevalence of CRSwNP than

did those without the allele [31,32]. A recent study [33] showed that serum periostin level is a potential biomarker of AERD, especially AERD with CRSwNP. Further work on the genetic mechanisms of the disease, and useful biomarkers, is required to improve the diagnosis of AERD and treatment of the upper airway. As AERD is not an IgE-mediated disease, skin tests detecting allergies are often negative in AERD patients [2]. However, such tests may distinguish AERD from allergic asthma.

TREATMENT

Patient education and counseling to ensure absolute avoidance of COX-1 inhibitors, with identification of well tolerated alternative drugs, are core features of AERD management, as are medical and surgical treatment of the underlying asthma and CRSwNP [4[■]]. Highly selective COX-2 inhibitors such as celecoxib are well tolerated alternatives, and acetaminophen (up to 1000 mg) and meloxicam (up to 15 mg) can also be well tolerated by AERD patients [4[■],34].

PHARMACOLOGICAL TREATMENT

Maintenance medications are required to control eosinophilic inflammation of the upper airway in AERD patients; these improve lower airway symptoms and asthma control status. Intranasal steroids are widely used as maintenance medications and are also effective to prevent relapse after surgery [3]. Leukotriene receptor antagonists and 5-lipoxygenase inhibitors play established therapeutic roles in patients with asthma and allergic rhinitis [35]. Such medications have also been widely prescribed to treat upper and lower airway symptoms in AERD patients; the drugs are used as add-on therapies to standard medications because overproduction of CysLTs is a key feature of AERD pathogenesis [36]. However, good evidence for a selective role played by leukotriene modifiers used to treat CRSwNP in AERD patients is lacking, although such modifiers (mainly montelukast) exhibit some effect when used to improve sinus status and quality-of-life parameters in CRS patients with or without NP [35].

SURGERY

Sinus surgery to treat CRSwNP is considered when medical treatment fails. Functional endoscopic sinus surgery is well tolerated and exhibits long-term efficacy, in CRS patients with or without NP [37]. Furthermore, functional endoscopic sinus surgery has been reported to improve lung function, asthma symptom scores, and nasal symptoms and

reduce systemic steroid use, in asthma patients with CRSwNP, although such effects were not always significant in AERD patients [38,39]. In AERD patients, CRSwNP exhibits a tendency to recur after surgery that is up to 10-fold higher than that of patients with other forms of CRSwNP [39,40].

ASPIRIN DESENSITIZATION

Although all AERD patients can be desensitized to aspirin, such desensitization is recommended for those with uncontrolled NP disease requiring more than one operative intervention, repeated or continuous use of systemic corticosteroids, or daily use of aspirin, or other nonselective COX inhibitors [1,4[■]]. The therapeutic effects of aspirin desensitization in AERD patients have been described in many studies [41–45] and include significant improvements in nasal symptoms and asthma control, decreased NP formation and sinus infection, reduced sinus surgery, and reduction in the need for systemic corticosteroids.

Most studies [42–45] on aspirin desensitization via daily exposure to aspirin showed that a maintenance dose of aspirin (650 mg twice per day) was relatively well tolerated. In general, the long-term efficacy of aspirin desensitization becomes apparent at 4 weeks [45], and has been confirmed to last up to 6 years [42–44]. Long-term clinical studies [42–44] indicate that between 67 and 87% of patients both tolerate and derive benefits from daily aspirin therapy, whereas 13% could not continue aspirin therapy because of side-effects such as gastritis, bleeding, or asthma flare-up. Aspirin 600 mg once daily for 4 weeks, given as a maintenance dose, was also associated with significant improvements in nasal and asthma symptoms [46]. Aspirin 300 mg once daily has recently been reported to reduce the annual consumption of systemic corticosteroids, and to reduce the need for surgery. Nasal and sinus symptoms did not improve when aspirin was given at 100 mg once daily [41,47[■]]. It is recommended to commence aspirin at 650 mg twice daily for 1 month, and then to titrate the dose down by 325 mg per month, as tolerated [4[■]]. The mechanism of aspirin desensitization is not fully understood. Such desensitization was shown to decrease production of CysLTs and to downregulate CysLTR1 expression. Direct inhibition of the IL-4-activated STAT6 pathway upon repetitive aspirin ingestion has also been described [48]. Furthermore, sputum IL-4 levels decreased in AERD patients 6 months after desensitization [49]. Aksu *et al.* [50[■]] recently showed that aspirin desensitization decreased CD4⁺ IFN- γ and IL-10 levels after 1 month of treatment, suggesting that expression of these modulators by

CD4⁺ T lymphocytes may be associated with desensitization. This seems consistent with the recent finding that increased levels of IFN- γ in AERD patients promoted maturation and activation of eosinophils and triggered eosinophil-related gene expression [19[■]].

CONCLUSION

Further work is required if we are to understand arachidonate dysregulation and the activation mechanisms of eosinophils in the upper airway mucosa of AERD patients. In future, biological agents such as anti-IL-5 or anti-IgE antibodies may be useful therapeutic agents for CRSwNP in AERD patients [51,52]. Further trials are essential to validate the use thereof.

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Conflicts of interest

There are no conflicts of interest.

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