ORIGINAL ARTICLE

Aspirin-Exacerbated Asthma

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This review focuses on aspirin-exacerbated asthma (AEA). The review includes historical perspective of aspirin, prevalence, pathogenesis, clinical features and treatment of AEA. The pathogenesis of AEA involves the cyclooxygenase and lipooxygenase pathway. Aspirin affects both of these pathways by inhibiting the enzyme cycooxygenase-1 (COX-1). Inhibition of COX-1 leads to a decrease in prostaglandin E2 (PGE2). The decrease in PGE2 results in an increase in cysteinyl leukotrienes by the lipooxygenase pathway involving the enzyme 5-lipooxygenase (5-LO). Leukotriene C4 (LTC4) synthase is the enzyme responsible for the production of leukotriene C4, the chief cysteinyl leukotriene responsible for AEA. There have been familial occurences of AEA. An allele of the LTC4 synthase gene in AEA is known as allele C. Allele C has a higher frequency in AEA. Clinical presentation includes a history of asthma after ingestion of aspirin, nasal congestion, watery rhinorrhea and nasal polyposis. Treatment includes leukotriene receptor antagonists, leukotriene inhibitors, aspirin desinsitaztion and surgery. AEA is the most well-defined phenotype of asthma. Although AEA affects adults and children with physician-diagnosed asthma, in some cases there is no history of asthma and AEA often goes unrecognized and underdiagnosed.

Key words: *aspirin desensitization, aspirin exacerbated asthma, aspirin exacerbated respiratory disease, aspirin sensitive asthma, cysteinyl leukotriene, leukotriene, leukotriene C4, leukotriene C4 synthase*

Acetylsalicylic acid (aspirin) is one of the most prescribed and frequently used over-the-counter medications of all time. Aspirin-exacerbated asthma (AEA) was first reported 84 years ago after severe bronchospasm in an individual with asthma was observed following aspirin ingestion and is characterized by eosinophilic rhinosinusitis, nasal polyposis, aspirin sensitivity, and asthma.[1,2] All cyclooxygenase-1 (COX-1) inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, induce bronchospasm, rhinorrhea, and nasal obstruction in these subjects.[2–4] In addition, the ocular administration of the COX-1-inhibiting NSAID ketorolac has been linked to AEA.[4] Individuals with AEA usually have moderate to severe persistent asthma and often require treatment with high-dose inhaled corticosteroids and even systemic corticosteroids in some instances.[2,5] Although the exact mechanism causing the AEA has yet to be fully elucidated, there is considerable evidence that an alteration in the metabolism of arachidonic acid is responsible.[5–8]

Another clinical entity, chronic idiopathic urticaria with aspirin sensitivity, although perhaps similar at a biochemical level to AEA, is clinically different as this reaction is confined to the skin and subcutaneous tissues.[9] This review focuses on AEA.

Historical Perspective and Background

The medicinal properties of the group of alkali metal salts and esters known as salicylates have been known since ancient times. Records dating back to the time of Hippocrates (460 BC) describe powders derived from the bark of the white willow tree (*Salix alba*) used for pain relief; the name salicylic acid is derived from *Salix*, the Latin name for this tree.[10–13] In 1853, the French chemist Gerhardt neutralized salicylic acid by buffering it with sodium salicylate and acetylchloride, creating acetylsalicylic acid or aspirin. The discovery of aspirin by Gerhardt was abandoned until Felix Hoffman, a German chemist, rediscovered it in 1887 and learned of its unique property of reduced gastrointestinal irritation compared with

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salicylic acid. Shortly afterward, ''aspirin'' was patented by Bayer in 1889 as a new analgesic wonder drug. The reduced gastrointestinal irritation can be attributed to the acetylation of the phenolic hydroxyl group (-OH) of sodium acetylate.[14]

Salicylic acid was synthesized by Kolbe, a German chemist, in 1874 and was used as a analgesic; however, severe gastrointestinal irritation was a common side effect. In 1876, MacLagan and Stricker demonstrated that salicylic acid was an effective treatment for rheumatic fever; it was used later for chronic rheumatoid arthritis and gout.[15]

Table 1. Historical Perspective of Aspirin and Aspirin-Exacerbated Asthma

Date	*Person*	*Discovery*
460 BC	Hippocrates	Described properties of powders derived from bark of white willow tree (*Salix alba*)
1853	Gerhardt	Created ASA by acetylation of phenolic hydroxyl group of salicylic acid
1874	Kolbe	Synthesis of salicylic acid, used as a painkiller, although with severe GI side effects
1889	Hoffman	Rediscovered the medicinal properties of ASA without GI irritation; mass marketing by Bayer
1922	Abrami and Lemoyez	Reported a case of anaphylaxis to 100 mg ASA
1967	Samter and Beers	Reported the phenomena of ASA intolerance, nasal polyposis, asthma
1967	Vanselow	Bronchial asthma induced by indomethacin
1971	Sir John Vane	Identified mechanism of action of ASA as inhibition of cyclooxygenase pathway
1973	Lockey et al	Reported mechanism of the mode of inheritance of AEA as autosomal recessive
1980	Stevenson	Reported successful desensitization to ASA
1994	Szczeklik	Reported eicosanoids (cysteinyl leukotrienes) in pathogenesis of AEA

AEA = aspirin-exacerbated asthma; ASA = acetylsalicylic acid; GI = gastrointestinal.

Today salicylic acid and its derivatives have a variety of clinical uses. Salicylic acid is often used because of its keratinolytic properties as a topical solution for acne, cutaneous exfoliation in chemical skin peels, and psoriasis and for treatment of cutaneous fungal infections.[16] Aspirin is used as an analgesic and to treat fever, migraine, rheumatic fever (drug of choice), Kawasaki disease (along with intravenous immunoglobulin), pericarditis, and even ulcerative colitis (5-acetylsalicylic acid or mesalamine).[17] In addition, it is used to prevent coronary artery disease and for both primary and secondary prevention of cerebrovascular accidents.[18]

However, serious side effects are associated with its use, such as occurs in AEA. There are both short- and long-term side effects of aspirin, such as nephropathy, gastritis, peptic ulcer disease, prolonged bleeding, and Reye syndrome.[19,20] AEA was first described by Widal and colleagues in 1922. In 1967, Samter and Beers reported and popularized the phenomenon of AEA (Table 1).[21]

Definition

Over the past several decades, AEA has also been referred to as the Samter triad, aspirin triad, aspirin-sensitive asthma, aspirin-intolerant asthma (ATA), aspirin sensitivity, and aspirin-exacerbated respiratory disease. AEA best defines this phenomenon as this term describes the disease in which the exacerbation of asthma occurs following the ingestion of aspirin and other COX-1 inhibiting NSAIDs. AEA is used to refer to this syndrome throughout this article.[22,23]

Prevalence

Jenkins and colleagues found that prevalence rates are 21% and 5% for asthmatic adults and children, respectively, when examining primarily unblinded oral provocation tests in a systematic review of 66 articles on AEA.[24] Prevalence was dependent on the method used to diagnose AEA, with patients' histories alone giving a much lower prevalence rate of 2.7% in adults and 2% in children. In 1967, Vanselow first reported AEA exacerbated by indomethacin.[3] Jenkins and colleagues confirmed the finding that some other NSAIDs also exacerbated AEA by reporting the sensitivity to ibuprofen, $<$ 400 mg, of 98%; naproxen, 100 mg, of 100%; and diclofenac $<$ 40 mg, of 76 to 100%.[24] Vally and colleagues reported that the prevalence of respiratory symptoms triggered by aspirin in three different asthma study populations surveyed in Australia was 10 to 11%.[25] In a random sample by postal

survey of 4,300 adults in southern Finland, the prevalence of AEA reported in the general population was 1.2%; however, individuals with pre-existing physician-diagnosed asthma had reported prevalence rates of 8.8%.[26] A database study from Poland in which 12,971 adults were randomly selected showed a prevalence of AEA of 0.6% in the general population and 4.3% of subjects with a known diagnosis of asthma.[27] With nasal polyps, aspirin sensitivity may be as high as 14 to 22%, and with chronic rhinitis, it is 0.7 to 2.6%.[28] AEA may be widely underdiagnosed; for example, in the European Network of Aspirin-Induced Asthma (AIANE), 18% of participants were unaware of aspirin sensitivity before undergoing unblinded aspirin provocation tests. The reasons for underdiagnosis may be the lack of recognition by the AEA individual of mild symptoms induced by aspirin and low clinical awareness of this syndrome among health care professionals.[29] A study by Lockey and colleagues showed that if subjects are not double-blind challenged, the results may be falsely positive. Only one of three of the individuals challenged had positive results when tested using double-blind, controlled challenges. Therefore, without double-blinded challenges, the true prevalence of AEA cannot be ensured.[30]

Pathogenesis

An immunoglobulin E (IgE) mechanism does not explain the AEA phenomena. An elevated total IgE, dermographism, and increased sensitivity to antibiotics were associated with AEA in one study, but skin test responses with lysine-aspirin were negative. No antibodies against aspirin or other NSAIDs have been consistently detected in this disease.[2,31–35]

In 1971, Vane added credence to the theory that aspirin-precipitated attacks are not due to an allergic reaction but to inhibition of COX-1 in the airways when he discovered that aspirin inhibited the COX-1 enzyme.[36–41] That discovery led to the AEA COX pathway theory.

Some studies demonstrated an increase in the number of bronchial submucosal mast cells in AEA compared with ATA, whereas others have not confirmed this finding.[42,43] The cytokine profile of the mast cell was investigated in another study and reported an increase in bronchial submucosal mast cells expressing interleukin-5 and granulocyte-macrophage colony-stimulating factor.[44] Cowburn and colleagues did not report any significant differences in bronchial mucosal mast after lysine-aspirin challenges between ATA and AEA individuals even though the number of mast cells was lower in both groups when compared with healthy controls.[45]

Cyclooxygenase Pathway

Phospholipids are a class of lipids formed from four components: a fatty acid, a negatively charged phosphate group, nitrogen-containing alcohol, and a backbone of either glycerol or sphingosine. Four different groups of phospholipases exist, A, B, C, and D, with each group serving a unique function. Phospholipase A_2 produces arachidonic acid. It is from arachidonic acid that various eicosanoids are produced from the action of lipoxygenase and cycloxygenase, namely leukotrienes and prostanoids.

There are two main COX enzymes, COX-1 and COX-2, encoded by two specific genes on chromosomes 9q32 and 1q25, respectively. COX-3 also exists, and two smaller forms of COX-1, derived from alternative splicing of COX-1 messenger ribonucleic acid (mRNA), have been identified.[46] COX-2 is activated during periods of inflammation, whereas COX-1 is active during periods of quiescence.

The inhibition of COX-1 by aspirin causes the reactions associated with AEA, and this inhibition leads to a decrease in the production of prostaglandin E_2 (PGE_2), which acts like a brake on the uncontrolled synthesis of cysteinyl leukotrienes (Cys-LTs).[47–53] Picado and colleagues found decreased COX-2 mRNA expression by analysis of nasal polyps in subjects suffering from AEA.[48] Since COX-2 was found to be underexpressed, inadequate COX-2 regulation may also be involved in the pathogenesis of AEA.

NSAIDs that are highly selective for COX-2, for example, celecoxib and rofecoxib, do not cause acute exacerbations of asthma in AEA.[54,55] Cowburn and colleagues demonstrated that although aspirin removes PGE_2-dependent suppression in all subjects, only in AEA is there an increase in leukotriene C_4 (LTC_4) synthase, leading to a marked overproduction of Cys-LTs.[45]

Lipoxygenase Pathway and Production of Cys-LTs

Arachidonic acid is first converted by 5-lipoxygenase (5-LO) into 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and then into leukotriene A_4 (LTA_4). LTA_4 is converted into leukotriene B_4 (LTB_4) by the enzyme LTA_4 epoxide hydrolase. Eosinophils, mast cells, and alveolar macrophages use the enzyme LTC_4 synthase to conjugate glutathione with LTA_4 to make LTC_4. LTC_4 can be transported out of the cell and its glutamic acid moiety

removed by ubiquitous enzymes to make leukotriene D_4 (LTD_4). LTD_4, in turn, can be cleaved by dipeptidases to make leukotriene E_4 (LTE_4). LTC_4, LTD_4, and LTE_4 make up the Cys-LTs. The Cys-LTs cause bronchoconstriction, mucus plugging and edema, and cellular infiltration and recruitment in the airways. The overexpression of Cys-LTs occurs in both bronchial and nasal mucosa in AEA.[47–53]

In a study by Adamjee and colleagues, eosinophils from nasal polyps, immunopositive for LTC_4 synthase, were fourfold more numerous in AEA than in ATA. There were also threefold more cells expressing 5-LO in the nasal polyp mucosa. These investigators found that fivefold higher eosinophil counts accounted for the increased LTC_4 synthase expression in polyps from AEA.[53]

The inhibitory effect of PGE_2 in AEA was also investigated in a study that showed that inhaled PGE_2 affords almost complete protection in AEA by blocking aspirin-induced bronchoconstriction. The inhibitory effect, however, is still controversial as PGE_2 levels have been found to be both increased and decreased in nasal and bronchial lavages (Figure 1).[52,56,57]

Familial Inheritance

Lockey and colleagues in 1973 described four members of a Mennonite family with AEA, three of whom were first cousins.[58] One of the cousins, whose husband was a member of the isolate, had twin daughters, one with AEA and another with allergic rhinitis and extrinsic asthma but no AEA. The twin with AEA and her husband shared common ancestors in the eighth ancestral generation. The presence of AEA in relatives, influenced by the presence of consanguinity, suggests an autosomal recessive mode of inheritance. It also suggests that the discordance seen in the twins may be an indication of environmental influences on the phenotypic expression of this phenomenon.[58] Also mentioned in this article was a report of two sisters of a non-Mennonite family who had AEA and a third sibling with intrinsic asthma who improved after aspirin ingestion. Curiously, there are other case reports of AEA improving after aspirin ingestion.[30]

Miller described a pair of sisters with the AEA in another report of familial inheritance.[59] Von Maur and colleagues described a family with mild AEA and suggested a dominant mode of inheritance.[60] In this study, an early onset of asthma in most affected members of the family and a lack of symptoms of sinusitis or nasal polyposis predominated.

Familial occurrence of AEA was reported in 5.1% of 400 subjects studied in AIANE.[29] In these families, affected individuals were usually siblings. Szczeklik and Sanak reported on two sisters, aged 20 and 27 years, who, after being given unblinded aspirin challenges, had widely different reactions, with the older sibling experiencing an asthma exacerbation and the younger marked nasal congestion.[61] Both sisters shared the variant allele of LTC_4 synthase associated with AEA. The parents of the twins and some other family members who were atopic or had moderate eosinophilia were challenged with aspirin and had negative responses.

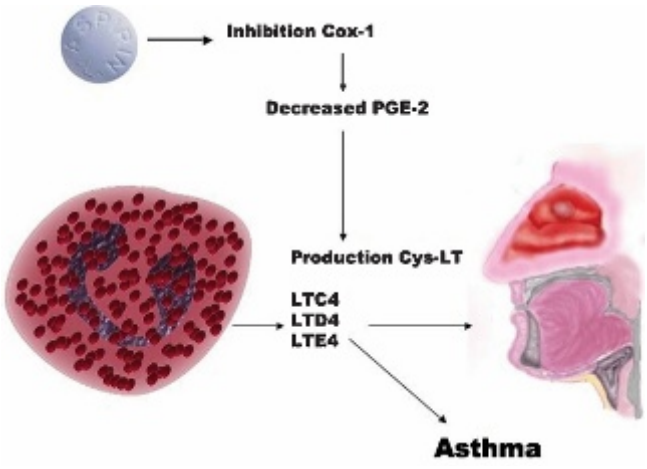

Figure 1. Cox-1 = cyclooxygenase-1; Cys-LT = cysteinyl leukotriene; LTC_4 = leukotriene C_4; LTD_4 = leukotreine D_4; LTE_4 = leukotriene E_4; PGE-2 = prostaglandin E_2.

LTC_4 Synthase

LTC_4, one of the Cys-LTs, is proposed as the primary leukotriene that causes bronchospasm in AEA.[48] Cys-LTs are first synthesized by 5-LO and 5-lipoxygenase-associated protein (FLAP 5). Expression of 5-LO is modulated by a genetic variation in the transcription factor binding motif of the 5-LO gene. No association between the allelic variants of 5-LO gene promoter and AEA has been observed, nor has there been any difference in the results from immunostaining of bronchial biopsy specimens for 5-LO and FLAP 5.[53,62]

LTC_4 synthase is a terminal enzyme that mediates production of Cys-LTs.[45,53,63] This enzyme is expressed in eosinophils, basophils, and macrophages. In these cells LTC_4 synthase alternatively converts LTC_4 from LTA_4. LTC_4 is rendered powerless owing to the lack of

concomitant 5-LO expression in platelets and epithelial and endothelial cells. Production of LTC_4 synthase depends on external sources of LTA_4.

LTC_4 synthase has been cloned by Lam and colleagues[68] and its function and sequence studied. An allelic variant of the LTC_4 synthase gene has been identified and is referred to as allele C. This allele has a 39% to 50% or higher frequency in AEA, 26% in ATA, and 25% in normal individuals. Allele C is formed by the transversion of adenine to cytosine, 444 bases from the translation start. Semiquantitative studies by Sanak and colleagues of LTC_4 synthase transcripts in peripheral blood eosinophils showed increased numbers of mRNA copies in individuals with AEA.[64] The increased transcripts correlated with the allelic C variant.

The nature of this interaction has yet to be fully elucidated. Of note, the transient increase in urinary LTE_4 in AEA following oral aspirin provocation has been observed only in allele C variants.[64] A Japanese study also showed that the variant C allele is higher in AEA than in ATA.[65]

Clinical Presentation

The age at onset of 300 subjects with AEA in the United States was, on average, 34 years. In women, the age at onset is usually earlier than in men, and severity is usually classified in the moderate to severe persistent category. Presentation in one European study showed a characteristic sequence of symptoms, first beginning with persistent rhinitis at around age 30 years of age and followed by asthma, aspirin sensitivity, and then nasal polyposis. Atopy was reported in one-third of cases.[66]

Rhinorrhea and nasal congestion are usually the first symptoms of AEA and are commonly refractory to pharmacologic therapy. It becomes perennial and more difficult to treat and then becomes associated with anosmia, recurrent and chronic sinusitis, and nasal polyposis.[5,6,66,67]

After the ingestion of aspirin or other COX-1 inhibitors, bronchospasm occurs within 1 to 3 hours. Care must be taken to differentiate selective COX-2 inhibitors from preferentially selective COX-2 inhibitors such as rofecoxib, meloxicam, and ibuprofen.

Preferentially selective COX-2 inhibitors are selective for COX-2 at low doses but at higher doses also inhibit COX-1.[68–70] However, despite their overall safety profile, caution must be used with these medications as several cases have been described in which bronchospasm occurred with their use.[71] Bronchospasm with COX-1 challenge can be accompanied by profuse rhinorrhea, conjunctival injection, a scarlet flushing of the head and neck, periorbital edema, abdominal pain, and even urticaria.[5,6]

A refractory period to the administration of aspirin or other COX-1 inhibitors develops after sufficient quantities of one or another of these medications is given to an AEA subject. This refractory period lasts for an average of 2 to 4 days.[30,72–74]

Diagnosis

AEA should be suspected when the following exists:

1. A history of exacerbation of asthma after ingestion of aspirin or other non-NSAIDs
2. Chronic and intractable nasal congestion and watery rhinorrhea, especially if specific IgE tests are negative
3. Nasal polyposis
4. Total or near-total opacification of the sinus cavities as demonstrated by computed tomography
5. An individual with the rapid onset of a severe attack of asthma with no previous insult who necessitates acute emergency care, intensive care unit admission, or endotracheal intubation[2,5,6]

The oral challenge, beginning with small amounts of aspirin and increasing the dose, is commonly used to confirm the diagnosis. Threshold doses of 30 to 150 mg (averaging 60–75 mg) evoke positive reactions and are the most sensitive diagnostic tool. Inhaled bronchial challenged with acetylsalicylic acid–lysine is also used to detect this syndrome. So, too, is nasal provocation with aspirin-lysine, but this technique is much less sensitive than bronchial challenge. Urinary LTE_4 can also be measured following aspirin challenge as an adjunctive measure to confirm a positive bronchial challenge.[75] Preferably, aspirin challenge tests should be preceded by a ''placebo challenge'' to exclude the variability of bronchial responsiveness; however, as with any study, double-blinded control studies are ideal.[2,5,6,66] Stevenson and colleagues also reported that intranasal ketorolac administration is a reasonably accurate and safe method to diagnose AEA.[76]

Prevention

AEA subjects should avoid all aspirin-containing compounds and other analgesics that have the potential to inhibit the COX-1 enzyme. They can safely ingest sodium salicylate, salicylamide, choline magnesium trisalicylate,

benzydamine, chloroquine, azapropazone, and dextropropoxyphene. However, these drugs are poor analgesics and have little anti-inflammatory effect.[77] Most individuals can ingest acetaminophen, which primarily inhibits COX-3 while weakly inhibiting COX-1 and COX-2. However, in some subjects, very sensitive to low provoking doses of aspirin, acetaminophen-induced asthma is more common. It can cause bronchoconstriction at doses greater than 1,000 mg in 34% of individuals with this syndrome.[78]

Treatment

The guidelines used to treat and manage AEA are no different from those used to treat moderate to severe persistent ATA asthma. Individuals with AEA occasionally require systemic corticosteroids in addition to their regular maintenance therapy.

Leukotriene inhibitors, such as zileuton, which inhibits 5-LO, and leukotriene receptor antagonists, such as montelukast and zafirlukast, are used to treat AEA. However, ATA and AEA subjects on leukotriene inhibitors have similar clinical outcomes, and urinary LTE_4 cannot be used to determine responses to these medications.[79,80] AEA subjects with the C allele appear to have a better response with leukotriene receptor antagonists.[81]

Surgery for nasal polyposis associated with AEA results in an 80% subjective improvement rate with a 40% chance or more of recurrence of nasal polyps and persistence of nasal symptoms. Thus, following sinus surgery, treatment with topical and systemic corticosteroids, aspirin desensitization, and leukotriene inhibitors is recommended.[88,89] Mild to marked improvement in quality of life was reported in individuals with AEA following sinus surgery in a Japanese study.[82] McFadden and colleagues also reported improvements in quality of life and pulmonary function tests (PFTs) and a reduction in systemic and topical corticosteroid requirements.[83] Simple polypectomy alone does not seem to be as useful as endoscopic surgery owing to the excessive amount of polypoid tissue burden in AEA.[2,84,85]

Aspirin Desensitization

Desensitization became possible because of the discovery of the refractory period in AEA.[30,72] Stevenson and colleagues, in 1980, reported on two individuals with AEA who were successfully desensitized to aspirin.[86] They were continuously treated with daily aspirin, and both individuals reported improvement in nasal patency, with one regaining her sense of smell. Therapy with aspirin was continued for months, with persistent nasal airway patency and a diminished growth in nasal polyps, with an overall reduction of half in the use of systemic corticosteroids and improvement in rhinitis and asthma.

In another study by the same investigators, published in 2003, of 172 subjects, 67% experienced a reduction in their nasal airway symptoms and systemic and corticosteroid requirements as long as they maintained their daily intake of aspirin. In 126 subjects who completed a year or more of such treatment, 87% experienced good or excellent improvement in sense of smell and general assessment of nasal-sinus and asthma symptoms. This study suggests that aspirin desensitization be used for those who do not respond to topical glucocorticoids or oral leukotriene antagonists. Those ideal for desensitization have nasal polyposis, necessitating treatment with systemic corticosteroids.[86,87]

Sousa and colleagues reported that desensitization is associated with a reduction in the number of inflammatory cells in the nasal mucosa expressing the Cys-LT1 receptor and that downregulation of receptor expression after aspirin desensitization is the likely mechanism of action.[88] Pretreatment with Cys-LT receptor antagonists prior to aspirin desensitization significantly decreases the risk of AEA.[89,90]

Other new modalities are under investigation, some involving high-dose aspirin therapy for emergent desensitization using oral protocols based on rapidly escalating doses of aspirin. In individuals with aspirin-induced urticaria-angioedema, a separate clinical entity with perhaps similar pathogenic mechanisms, Wong and colleagues reported the safe, rapid oral challenge desensitization to aspirin.[91] In this study, aspirin administration permitted individuals with coronary artery disease to receive aspirin. Some other promising treatments, such as tacrolimus, have proven ineffective.[92]

Conclusion

AEA is perhaps the most well-defined asthma phenotype compared with other asthma phenotypes, such as allergic, non-allergic, exercise-induced, and infectious asthma. It is a relatively common phenotype of asthma, affecting primarily adults but also children with physician-diagnosed asthma and, in some cases, subjects with no previous history of asthma. It is often unrecognized and underdiagnosed.

Subjects with moderate to severe asthma who have severe nasal congestion, nasal polyposis, and radiologic evidence of opacification of sinuses and who require emergent care and/or intubation should be suspected to

have this form of asthma. A history of exacerbation associated with the ingestion of aspirin or other COX-1 NSAIDs can be diagnostic for the phenotype. A refractory period following aspirin challenge during which no additional symptoms occur with additional aspirin or other COX-1 NSAIDs may last up to 2 to 4 days.

PGE_2 acts as a brake on LTC_4 synthase, which moderates the production of Cys-LTs. Individuals with AEA have decreased levels of PGE_2, which, in turn, causes an overproduction of Cys-LTs, which theoretically causes AEA. Genetic mechanism studies suggest that there is a familial incidence; however, the exact mode of inheritance is unknown.

Treatment of AEA primarily involves use of systemic and inhaled glucocorticosteroids, short- and long-acting β-agonists, leukotriene-modifying agents, and medical and sometimes surgical treatment of the rhinitis and/or nasal polyposis.

Leukotriene-modifying agents and inhaled corticosteroids, often in high doses, are the mainstay of therapy. Aspirin desensitization is also a useful tool and in up to 60 to 70% of these patients, and the response sometimes can be dramatic in reducing the overall dependence on inhaled and/or systemic glucocorticosteroids.

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