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Aspirin Induced Asthma- a Review

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Abstract: Asthma is currently a worldwide problem. Worldwide deaths from this condition have reached over 250,000 annually. Aspirin or Acetylsalicylic acid (ASA), has remained one of the world's safest, least expensive and most consumed analgesics. Aspirin (other Nonsteroidal anti-inflammatory drugs; NSAIDs) is contra-indicated for asthmatics because aspirin (other NSAIDs) precipitate asthmatic attacks in patients with bronchial asthma. Aspirin-induced asthma (AIA) refers to the development of acute bronchoconstriction, profuse rhinorrhea and skin flushing in asthmatic individuals following the ingestion of aspirin. The prevalence of AIA is 4.3, 8.8 and 10.5% in Poland, Finland and Australia, respectively. AIA is more common in women. The biochemical pathways involved in aspirin-sensitive asthma are not fully established. In this review, we try to provide an overview of pathogenesis, clinical symptoms, diagnosis & treatment of AIA.

Key words: Aspirin-induced asthma · Aspirin · Bronchoconstriction · Cyclo-oxygenase pathway · lipoxygenase pathway

INTRODUCTION

Asthma is a life threatening chronic disease of the respiratory system, well known as paroxysmal attacks of bronchospasm. It is very common among children & adults, but asthmatic attacks can start at any age. Asthma is currently a worldwide problem. Around 300 million people around the globe suffer from asthma and this number is rising. Worldwide deaths from this condition have reached over 250,000 annually [1]. There are mainly 3 types of asthma: intrinsic (non-allergenic/non-atopic/non-immunologic), extrinsic (allergenic/ atopic/immunologic) and mixed (elements of both). However, asthma is not a homogenous entity and many subtypes of asthma exist according to precipitating factors such as:

- Allergy (atopic versus non-atopic asthma)
- Work exposure (occupational asthma)
- Exertion (exercise-induced asthma)
- Infection (viral-induced asthma) and
- Drugs (aspirin-induced and steroid ressistence asthma)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed, out of which, aspirin or Acetylsalicylic acid (ASA), has remained one of the world's safest, least expensive and most consumed analgesics [2]. Besides its analgesic and antipyretic properties, aspirin also possesses antiplatelet activity and therefore, it is used in patients of unstable angina and myocardial infarction, but on other hand, aspirin and other NSAIDs are reported to account for 21-25% of all adverse drug reactions [3]. Aspirin (other NSAIDs) is contra-indicated for asthmatics because aspirin (other NSAIDs) precipitate asthmatic attacks in patients with bronchial asthma [4]. Asthmatic patients who are sensitive to aspirin and possibly other NSAIDs, are commonly referred to as aspirin-sensitive asthmatics. Aspirin-induced asthma (AIA) was first described by Widal *et al*. [5]. Aspirin-induced asthma refers to the development of acute bronchoconstriction, profuse rhinorrhea and skin flushing in asthmatic individuals following the ingestion of aspirin [3]. It is also known as Aspirin-triod or Aspirin-intolerant asthma. The onset of asthma usually occurs 30 minutes to three hours after the person ingests aspirin [6].

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The first case of aspirin sensitivity in a patient with asthma was described in 1902, a few years after the introduction of aspirin into clinical use. In 1968, Samter and Beers described a triad consisting of asthma, aspirin sensitivity and nasal polyps, which came to be known as Samter's triad [7].

Prevalence: Aspirin-induced asthma is the acquired and oversensitive condition. Asthma and aspirin hypersensitivity develop 2 to 15 years later. Once developed, aspirin intolerance remains throughout life, although sporadic disappearance of intolerance has been reported [8]. Recently, three large population-based surveys of AIA were published from Finland, Poland and Australia. The prevalence of AIA is 4.3, 8.8 and 10.5% in Poland, Finland and Australia respectively [3, 9, 10]. Although, aspirin induced asthma has been considered rare in children, but prevalence is still around 5% when children are subject to oral provocation testing [11]. It has been appears after the puberty and occupies about 10 to 20% of adult asthma [12]. AIA is more common in women [13, 14]. It was observed that the onset of symptoms occurred significantly earlier and the disease was more progressive and severe in women than in men [15]. It was found that people with aspirin-induced asthma are not sensitive only to aspirin, but also showed cross sensitivity to all NSAIDs that inhibit cyclo-oxygenase (COX) enzymes [2]. The affected patients showed hypersensitivity to three other widely used non-steroidal, anti-inflammatory drugs namely, ibuprofen (Advil), naproxen and diclofenac. The rates of sensitivity were 98% for ibuprofen, 100% for naproxen and 93% for diclofenac. It was noted that only 7% were sensitive to acetaminophen and reactions to acetaminophen tend to be less severe as compare with other non-steroidal anti-inflammatory drugs [6].

AIA seems to be underdiagnosed worldwide. Approximately 15% of asthmatics and 34% of the patients with asthma and concomitant rhinosinusitis were unaware of aspirin hypersensitivity before the challenges. The reason for the underreporting of aspirin hypersensitivity may include the deliberate avoidance of NSAIDs by asthmatics aware of the risk of adverse reactions, or a lack of recognition by patients of mild NSAID-induced reactions because of their delayed onset of reaction [16, 17]. Underdiagnosis of aspirin sensitivity is also the result of the lack of routine aspirin challenge testing of asthmatic patients.

Pathogenesis: Asthma is an inflammatory condition of the airways. In this state of continuous inflammation, exposure to aspirin in a subset of asthmatic patients appears to temporarily accentuate the inflammatory process, leading to asthma exacerbations. The acute attack of asthma induced by aspirin is similar to the immediate hypersensitivity reaction, involving an antigen antibody reaction [18]. Therefore, hypersensitivity reactions to aspirin and other NSAIDs might be mediated by IgE-dependent mechanisms. However, the skin test responses with ASA lysine are negative as well as IgE antibodies against either aspirin or NSAIDs have not been found in patients receiving AIA. So, the hypersensitivity reaction might be mediated by IgE-independent mechanisms and hence, the reactions could be termed as anaphylactoid [19]. The biochemical pathways involved in aspirin-sensitive asthma are not fully established. However, aspirin hypersensitivity is likely to be mediated by a deviation of the arachidonic acid metabolic pathway toward excessive leukotriene (LT) production. Cyclo-oxygenase (COX) and lipoxygenase (LO) are two main pathways involved in the metabolism of arachidonic acid (AA).

The Cyclo-Oxygenase Pathway: The cyclo-oxygenase (COX) pathway converts arachidonic acid to prostaglandins, prostacyclin and thromboxane A_2 [20, 21]. There are two isoforms of COX, namely COX-1 and COX-2 [22]. COX-1 (Prostaglandin-H_2 synthase-1) (PGHS-1) is constitutively expressed in most tissues and blood platelets and involved in cellular housekeeping functions.COX-2 (PGHS-2) is induced by inflammatory stimuli such as growth factors, cytokines and mitogens in fibroblasts and by bacterial lipopolysaccharide in monocytes and macrophages and is thought to be involved in inflammatory functions [23 - 25]. The cyclooxygenase response to aspirin is altered in AIA [26]. Attacks of asthma precipitated by aspirin like drugs are due to the inhibition of COX in airways of the sensitive patients. Airway lavage fluid after ASA-lysine challenge showed significant decrease in PGE2 and thromboxane B2 (TXB2) level in aspirin-induced asthma (AIA) and asthmatics tolerant to aspirin (ATA) groups, however PGD2, PGF2α and PGF2 level decreased only in ATA patients [26]. It was suggested that asthmatic bronchospasm may be due to overproduction of the bronchoconstrictor PGF at the expense of the bronchodilator PGE2 due to altered COX response [27].

The airway mucosal biopsy study was performed in AIA individuals. Their results indicated that there was no difference between AIA and ATA groups with relation to COX 1 and COX 2 expression [28]. Prostaglandin E2 inhibits of inflammatory mediator release from mast cells, eosinophils and macrophages *in vitro* [29]. It slows down leukotriene synthesis and inhibits LTB4 and superoxide release from polymorphonuclear leukocytes [30, 31]. Depressed basal generation of PGE2 by epithelial cells from nasal polyps was observed in aspirin intolerant patients. Thus, aspirin/NSAIDs induced defective synthesis of PGE2 might be one of molecular disturbances observed in AIA and leading to the precipitation of asthmatic attacks. Alternatively, in the presence of aspirin, COX-2 is modified enzymatically to form 5-hydroxyeicosatetraenoic acid instead of PGs, especially prostaglandin E2 (PGE2) that inhibits leukotriene biosynthesis. 5- hydroxyeicosatetraenoic acid stimulates 5-lipoxygenase (5-LO) that generate 5-LO products and could account for the effects of AIA [32].

The Lipoxygenase Pathway: Oxygenation of arachidonic acid (AA) at position C-5 of the molecule is performed by two proteins-5-LO activating protein (FLAP) and 5-Lipoxygenase (5-LO). The FLAP transports arachidonic acid into the cytosol to be acted on by the enzyme 5-LO. The product of 5-lipoxygenation of AA, leukotriene A4 (LTA4), is released by granulocytes. LTA4, which is further hydroxylated to LTB4. LTB4 is a potent chemotactic agent for leucocytes and may be important in mediating the inflammatory process in asthmatic airways [33]. The enzyme leukotriene-C4 synthase (LTC4S), present in eosinophils, basophils, macrophages, platelets and mast cells, alternatively converts LTA4 to Cysteinyl-LTs (Cys-LTs). LTC4 is exported to the extracellular space where it forms LTD4, which in turn is cleaved to form LTE4, the 6-cysteinyl analog of LTC4. Both, LTD4 and LTE4 are excreted in the urine. The LTC4, LTD4 and LTE4 are known as sulphidopeptide leukotrienes. The sulphidopeptide leukotrienes are potent constrictors of the smooth muscle of the airways and may also contribute to the bronchial hyperresponsiveness characteristic of asthma [34, 35]. LTD4 can increase mucus production in human airway preparations and airway microvascular leakage in animals [36, 37]. The cysteinyl LTs exert their action through G-protein coupled receptors, CysLT1 and CysLT2. It has been suggested that aspirin-induced asthma may relate to the inhibition of cyclooxygenase, resulting in the "shunting" of arachidonate cascade to the 5- lipoxygenase pathway. This will lead to the increased generation of leukotrienes in susceptible individuals, which, in turn, cause bronchoconstriction [27]. The basal production Cys-LTs is 2 to 10-fold higher in AIA and baseline levels further increase significantly after oral or bronchial aspirin provocation [38]. It has been demonstrated that LT modifiers can effectively prevent aspirin-induced bronchoconstriction following aspirin challenge [39]. Significant quantities of LTC4 and LTE4 have been detected in the bronchoalveolar lavage fluid of symptomatic asthmatic patients compared with normal control subjects and increased quantities of leukotrienes have been detected in bronchoalveolar lavage fluid after local endobronchial challenge with allergen [40 - 42]. Subjects with aspirin-sensitive asthma have six times higher basal levels of urinary LTE4 than aspirin-tolerant asthmatic and nonasthmatic subjects [43]. Furthermore, aspirin challenge of subjects with aspirin-sensitive asthma, which leads to bronchoconstriction, is accompanied by fourfold increase in urinary LTE4 excretion. No clinical symptoms or increase in urinary LTE4 levels are detected in non-aspirin-sensitive asthmatic individuals following aspirin ingestion [43]. Additionally, there is increased target organ sensitivity to the bronchospastic effects of inhaled LTE4 in subjects with aspirin-sensitive asthma compared with aspirin-tolerant asthmatic subjects [44]. Ferreri *et al.* [45] measured mediator release in the nasal lavage fluids of aspirin sensitive asthmatic patients after aspirin challenge. The release of LTC4 into nasal secretions was noted but there was no decrease in the levels of prostaglandin E2 (PGE2). A genetic variant of LTC4 synthase gene promoter has been described, which is overexpressed in the AIA population [46]. The –444C allelic frequency was found significantly higher in severe AIAR patients as compared with ATA or healthy subjects and this group responded to aspirin challenge with significantly higher overproduction of cys-LTs as measured by urinary excretion of LTE4 [47]. Therefore, this allelic variant can predispose to severe form of AIA. This is further supported by bronchial biopsy studies. The overexpression of LTC4 synthase in bronchial biopsy specimens of patients with AIA is correlated with aspirin sensitivity and is fivefold higher than in subjects with ATA [48]. In contrast to overexpression of LTC4 synthase, 5-LO expression remain unaltered in patients with AIA precludes 5-LO as a contributing factor in the pathogenesis of AIA [49]. Leukotriene receptor antagonists inhibit asthmatic responses induced by aspirin as well as exercise [50-52]. Leukotriene receptor

antagonism also reduced allergen induced bronchial hyperresponsiveness [53]. As leukotrienes are critical in the asthmatic response provoked by aspirin, Zileuton (5- lipoxygenase inhibitor) protected against asthma induced by hyperventilation as well as attenuated aspirin induced asthmatic responses [54, 55].

Other Inflammatory Mediators

Lipoxins: Besides leukotrienes, the interactions between 5-lipoxygenase and 15-lipoxygenase on arachidonic acid metabolism generates a new series of biologically active metabolites described as lipoxins [56]. Unlike leukotrienes, lipoxins possess trihydroxytetraene structure and the stereochemistries of the two major isomers, lipoxin A4 (LXA4) and lipoxin B4 (LXB4) [57, 58]. Lipoxins can be generated by human neutrophils, eosinophils, or platelets during inflammatory responses [59, 60]. During the biosynthesis of lipoxins from arachidonic acid, leukotriene biosynthesis is blocked. Thus, there exists inverse relationship between leukotriene and lipoxin biosynthesis. The 15-lipoxygenase is abundant in lung tissue and that LXA4 has been detected in the bronchoalveolar lavage fluid of patients with asthma and other lung diseases suggests that LXA4 may be a potential mediator or modulator of inflammation in the lung [61]. LXA4 attenuated LTB4-induced neutrophil migration and plasma leakage and thereby exhibiting anti-inflammatory properties. The effect of LXA4 on neutrophil functions was associated with inhibition of phosphoinositide hydrolysis and calcium mobilization [62, 63]. Anti-inflammatory effect of lipoxin was equivalent to that of dexamethasone [64]. Moreover, LXA4 inhibits guinea pig pulmonary responses to LTC4 *in vitro* and inhalation of LXA4 in asthmatic subjects inhibited the bronchoconstrictor response to LTC4. Thus, LXA4 may modulate LTC4-induced airway obstruction and acts as an endogenous sulphidopeptide leukotriene receptor antagonist [65, 66]. Aspirin intolerant asthmatics seem to exhibit decreased capacity for generation of lipoxins [67].

Endogenous Nitric Oxide (NO) and Oxidative Stress: NO is an important cellular signaling molecule, having a vital role in many biological processes. Nitric oxide synthase (NOS) catalyzes the production of nitric oxide (NO) from L-arginine. There are three isoforms of the NOS enzyme: endothelial (eNOS/NOS-III), neuronal (nNOS/NOS-I) and inducible (iNOS/NOS-II) - each with separate functions. Basal synthesis is controlled by constitutive isoform of nitric oxide syntethase i.e endothelial NOS. NO is synthesized by epithelium of respiratory tract in small undetectable amounts and having probably homeostatic and protective function. Under inflammatory and pathological conditions, expression of inducible NOS is increased, mainly in inflammatory cells and myocytes and it is responsible for increased NO generation by lungs in inflammatory conditions [68, 69]. Pro-inflammatory action of NO is mediated through activation of enzymes like cyclooxygenase or metalloproteases [70]. In AIA patients, functional abnormality of COX leads to more severe inflammation [69]. Exhaled NO may indicate airway inflammation in patients with AIA. After lysine-aspirin (L-ASA) inhalation, fractional exhaled NO (FENO) increased significantly in patients with AIA, reaching the peak value 4 h after bronchoconstriction, while no change was observed in patients with ATA and in controls [71]. 8-Isoprostane, a stable prostaglandin-like arachidonate product formed on membrane phospholipids by the action of reactive oxygen species, is postulated to be a reliable *in vivo* biomarker of lipid peroxidation [72, 73]. The 8-Isoprostane in breath condensate appears to reflect oxidative stress and is progressively increased with the severity of asthma. Increased levels of 8-isoprostane was found in expired breath condensate in patients with AIA compared with healthy control subjects [74].

Inflammatory Cells: The cellular origin of mediators in an acute aspirin-induced bronchoconstriction episode remains uncertain. Increased number of eosinophils and mast cells were identified in blood, nasal and bronchial secretions as well as in bronchial biopsy specimens of patients afflicted with AIA [74]. In bronchial biopsies, eosinophils are fourfold more numerous than in aspirin-tolerant subjects with asthma and 15-fold more numerous than in normal biopsies [75]. Macrophages were also found throughout the respiratory tract, prominently in the bronchial wall and lumen [76]. The numbers of neutrophils and T-lymphocytes were similar in aspirin-sensitive asthmatic (ASA) subjects and non-aspirin-sensitive (non-ASA) control subjects [74]. A marked overexpression of the LTC4 synthase (the key enzyme in the Cys-LT pathway) was demonstrated in eosinophils and mast cells from bronchial biopsy specimens of many patients with AIA [77]. Thus, increased number of eosinophils and the presence of an increased amount of LTC4 synthase activity may be responsible for the pathophysiological change in AIA. IL-5 is the key regulator of eosinophil lineage and is involved in eosinophilopoeisis and in eosinophil recruitment, activation, maturation and survival enhancement.

The airway expression of IL-5 is also markedly increased in patients with AIA [78]. Thus, eosinophil infiltration of airway tissue appears to be a central feature of AIA. The constitutive (IgE-independent) activation of mast cells seems to be involved in mediator release and is crucial for understanding AIA. The micro-environmental conditions created by fibroblasts and/or eosinophils, enable mast cells to release their products through G-protein-coupled receptors [79, 80]. Although NSAIDs neither provoke activation of mast cells nor eosinophils, NSAIDs induced decrease in PGE_2 may lead to further release of mediators by already activated mast cells. In AIA patients, bronchial fibroblast had six fold lower PGE_2-biosynthetic capacity compared with healthy subjects and only one third that of aspirin-tolerant asthmatics [81].

Clinical Presentation: AIA developed according to a characteristic sequence of symptoms: persistent rhinitis appeared at an average age of 30 years and was followed by asthma, ASA sensitivity and nasal polyposis. Rhinorrhea and nasal congestion are usually the first symptoms of AIA. Asthma and sensitivity to ASA become manifest an average of 1 to 5 years after the onset of rhinitis [82]. After the ingestion of ASA or NSAIDs, an acute asthma exacerbation occurs within 3 h accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema and, sometimes, a scarlet flushing of the face and neck and occasionally periorbital edema, abdominal pain and minor degrees of urticaria [15]. Fifty percent of the patients with AIA have chronic, severe, corticosteroid-dependent asthma, 30% have moderate asthma that can be controlled with inhaled steroids and the remaining 20% of patients have mild and intermittent asthma. Atopy was recorded in one third of the AIA patients [83]. In severe cases, ASA precipitates of life-threatening attacks of asthma. Rarely, in patients who produce extremely high amounts of Cys-LT, myocardial ischemia may develop [84]. Ocular complications are a frequent comorbidity in AIA [85].

Diagnosis: Clinical picture and patient's history enable the physician to make a diagnosis AIA but in doubtful cases, Challenge tests with aspirin are the cornerstones of diagnosis and are considered to be the only reliable confirmation test available [86]. The accurate diagnosis of AIA can be established by oral, inhaled, nasal, or intravenous placebo-controlled provocation tests with increasing doses of aspirin [87-89]. Oral challenge with aspirin is most commonly performed than bronchial challenge test because it appears to be slightly more sensitive method (69-89%), than bronchial challenge test (60-77%). It also mimics the natural exposure to the drug, induces wider spectrum of clinical symptoms in patients with aspirin intolerance and the test does not require special equipment. However, the difference is not statistically significant [90]. In oral challenge test, positive reactions are evoked after the ingestion of 30 to 150 mg ASA (average, 60-75 mg). Bronchial challenge is less sensitive than oral test, but induces milder and usually local reactions. As it consumes less time than oral challenge test, this method is probably more suitable for studies on the influence of pharmacological agents on the asthmatic aspirin induced response [91]. In bronchial challenge, lysine-aspirin is administered by inhalation. Either challenge is considered positive if a fall in forced expiratory volume in 1 second of more than 20% occurs, accompanied by clinical symptoms. Tests should be performed by trained professionals in hospitals with full facilities for resuscitation. The nasal challenge with aspirin is quick, easy to carry out, less expensive and free of life threatening systemic or bronchial side effects [89]. A recent study confirmed high sensitivity and specificity of nasal aspirin challenge as evaluated by active anterior rhinomanometry (80 and 92.5% respectively) [92, 93]. It is recommended as a useful quick first-line *in vivo* test or in patients with unstable asthma.

The search for *in vitro* diagnostic tests continues. The tests, based on the release of Cys-LTs by peripheral blood leukocytes remain nonspecific, as reviewed recently [94]. On the other hand, new noninvasive methods, such as the assessment of eicosanoid levels in exhaled air condensate or induced sputum, might be developed in the future as an interesting diagnostic tool [95].

Treatment and Prevention: The general rules concerning treatment of AIA do not differ from the recently accepted guidelines for the management of asthma [96]. To prevent life-threatening reactions, patients should be advised to avoid aspirin and products containing aspirin. NSAIDs that cross-react with aspirin also should be avoided. Patients with AIA can safely take sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone and dextropropoxiphene. These drugs are weak inhibitors of COX or are devoid of anticyclooxygenase activity. Unfortunately, they have mild anti-inflammatory effects and are moderate analgesics [97, 98]. Nimesulide and meloxicam, which are predominantly COX-2 inhibitors, well tolerated by AIA patients in lower doses but they induced mild bronchial obstruction and rhinorrhea at high doses [99, 100].

Anti-LT drugs are being used currently in the treatment of patients with AIA [96]. These drugs either inhibit cys-LTs synthesis by blocking 5-LO (ie, zileuton) or its activator 5-LO-activating protein (FLAP) or block specific cys-LTs receptors (ie, zafirlukast, montelukast and pranlukast). Pretreatment with antileukotrienes prevented or attenuated the acute aspirin-precipitated nasal and bronchial reactions [101, 102]. However, recently it was reported that a higher therapeutic dose of aspirin overcame the protection from pretreatment with zileuton [103]. Anti-LTs also induce bronchodilation in patients with AIA. Good therapeutic efficacy on chronic treatment of AIA with anti-leukotriene drugs has been demonstrated in recent trials. It has been found that zileuton, montelukast and pranlukast provided short-term and long-term improvement in pulmonary function measurements compared to baseline in patients with AIA as well as reduce asthma exacerbations [104-106]. PGE2 produced by different cells of the bronchial mucosa, might be a powerful local protective factor preventing bronchoconstriction in response to numerous stimuli. Inhaled PGE2 attenuated bronchoconstriction precipitated by aspirin [107]. Misoprostol, an oral stable analogue of PGE1 caused the same effect, although its inhibitory potency was weaker than that of inhaled PGE2 [107]. Salmeterol, a long-acting b2-agonist also has been found to be effective in the management of AIA and also has attenuated the bronchial hyperresponsivenessto lysine-ASA [108]. Other agents were also tried with regard to usefulness in AIA therapy. Roxitromycin had anti-inflammatory effects, acyclovir prevented bronchoconstriction and cromolyn suppressed eosinophilic inflammation [109-111].

Patients with known aspirin/NSAID sensitivity who need to take aspirin or anti-inflammatory medications for treatment of other conditions, such as rheumatic diseases, degenerative joint diseases, migraines, chronic or recurrent headaches and arterial thromboembolic diseases, it is necessary to induce the state of aspirin tolerance and to maintain it by “aspirin desensitization” [112]. The state of “aspirin desensitization” is achieved by administration of increasing oral doses of aspirin over a period 2-5 days until the dose of 600 mg is achieved. Then, aspirin is given regularly at a daily dose of 600-1200 mg. After each dose of aspirin, there is a refractory period of 2-5 days duration, when aspirin and other NSAID can be taken. When aspirin is discontinued, the sensitivity gradually returns over 6-7 days to their pre-desensitization levels and this could precipitate an acute asthma attack on exposure to NSAIDs [113, 114]. During aspirin desensitization, gastritis as well as cutaneous reactions to aspirin was observed. Endonasal administration of lysine-ASA significantly reduced relapse rates of nasal polyps and thus, has been found to be effective in nasal polyposis induced by aspirin [114, 115]. It was reported that AIA becomes refractory by repeated provocation with lysine-ASA inhalation. This is termed as adaptive deactivation [116]. It was observed that a 20-fold decrease in bronchial airway responsiveness to inhaled LTE_4 occurred after ASA desensitization [117]. There might be downregulation of cys-LT receptors in such a way that even though LTs are available, they cannot induce an effector event [118]. There was a substantial decline in the peripheral monocyte synthesis of LTB_4 in AIA patients after aspirin desensitization [118]. The state of ASA tolerance might be the result of a depletion of mast cell mediators such as histamine and PGD2 [119].

Rhinosinusitis in AIA is a troublesome cause of morbidity and an important source of costs [120]. Topical corticosteroids are particularly effective in most of aspirin-sensitive patients with rhinosinusitis In severe cases, their use should be preceded by 7-10 days period of oral corticotherapy [121, 122]. The positive effects of treatment with antileukotriene drugs have been also observed [123]. In many patients surgical procedures are needed to relieve chronic sinusitis and to remove nasal polyps. As most of aspirin-intolerant patients suffer from diffuse polypoid growth, polypectomy alone should be avoided as the effects are short-lived [124]. Aspirin desensitization is now recommended as standard add-on therapy for rhinosinusitis. ASA desensitization treatment is particularly appropriate for preventing re-growth of nasal polypoid tissue and reducing the need for systemic corticosteroids. Further therapeutic studies should apply the objective assessment of nasal functions, such as rhinomanometry, acoustic rhinometry and radiologic examination [125].

CONCLUSION

Eventhough aspirin is one of the most consumed analgesic, it is contraindicated in asthmatic patients as it precipitate asthmatic attacks. Approximately 15% of asthmatics and 34% of the patients with asthma and concomitant rhinosinusitis were unaware of aspirin hypersensitivity and hence, the diaese seems to be underdiagnosed. The undrlying pathogenic mechanism of AIA is the deviation of the arachidonic acid metabolites from COX pathway toward the LO pathway, leading to excessive leukotriene (LT) production. Futher research is

required to explain the role of other inflammatory mediators as well as inflammatory cells involved in aspirin hypersensitivity. More precise pharmacologic approach is also required besides using LT-modifiers and aspirin desensitization.

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