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ASPIRIN-INDUCED ASTHMA: FEATURES OF DIAGNOSIS AND TREATMENT

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Abstract
Hypersensitivity to acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) is a pressing problem for physicians of many specialties who use these drugs for a wide range of diseases. Aspirin-induced asthma often manifests itself as a triad: bronchial asthma, hypersensitivity to ASA and NSAIDs, polypous rhinosinusitis. Aspirin-induced respiratory disease may be limited to isolated polypous and, less commonly, non-polypous rhinosinusitis. Diagnosis is based on anamnestic and clinical signs. In the absence of a typical anamnesis, the diagnosis of hypersensitivity to NSAIDs is confirmed using a provocative test. Treatment includes anti-inflammatory drugs (glucocorticosteroids, antileukotriene drugs), exclusion/limitation of triggers and, according to strict indications, desensitization of ASA, as well as a new direction – therapy with biological drugs (omalizumab, etc.).

Keywords: Aspirin-induced asthma, aspirin-induced respiratory disease, hypersensitivity to nonsteroidal anti-inflammatory drugs.

INTRODUCTION

By the beginning of the current century, the term AERD (aspirin-exacerbated respiratory disease) appeared, reflecting the understanding that bronchial asthma and rhinosinusitis in this pathology are closely related pathogenetically. In addition, cases of ASA intolerance in patients with rhinosinusitis without bronchial asthma have become known [3]. A new, relatively recently introduced concept – NERD (nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease) – emphasizes that the triggers in this pathology are not only ASA, but also other NSAIDs [4]. In accordance with modern concepts of the pathogenesis of NERD, it is proposed to replace the old term “intolerance to ASA and NSAIDs” with “hypersensitivity” (HS).

MATERIALS AND METHODS

The pathogenesis of aspirin-induced asthma (AAA) remains largely unclear to this day. According to its inflammatory phenotype, AAA is an eosinophilic disease, and according to its molecular (cytokine) endotype, it is a Th2-mediated (Th2-helper) pathology [5]. Like other types of asthma, AAA is a multifactorial disease.

Acetylsalicylic acid and NSAIDs are only two of the many triggers for AAA. There is a significant evidence base that the pathological reaction to NSAIDs in AAA (and NERD in general) is associated with a genetically determined disorder of AA metabolism [1]. Important mediators involved in the pathogenesis of AAA are cysteinyl leukotrienes (LT) – LTC4, LTD4, LTE4, which have proinflammatory and bronchoconstrictor properties and are formed in such patients via the 5-lipoxygenase (5-LO) pathway in excess quantities.

RESULTS AND DISCUSSION

There are two known types of COX – COX-1 and COX-2. Drugs-COX inhibitors are divided into 4 groups [2]:

1) selective COX-1 inhibitors (ASA);
2) COX-1 and COX-2 inhibitors (most “classical” NSAIDs);
3) predominantly selective COX-2 inhibitors – nimesulide, meloxicam;
4) specific (highly selective) COX-2 inhibitors – coxibs.

The anti-inflammatory, antipyretic and analgesic effect of ASA/NSAIDs is associated with inhibition of the synthesis of prostaglandins (PG) of various classes.

At the same time, predominantly selective COX-2 inhibitors and coxibs significantly less often cause symptoms of HS in patients with AAA. It is assumed that this is due to the fact that ASA and non-selective COX inhibitors inhibit PGE2 synthesis, while selective ones do not significantly affect its level. In recent years, much attention has been paid to the importance of PGE2 in the pathogenesis of AAA. With normal arachidonic acid metabolism, PGE2 inhibits 5-LO activity, LT formation, and activation of eosinophils and mast cells, i.e., it performs a regulatory function in tissue inflammation. A number of studies have obtained data on a decrease in PGE2 formation in the nasal epithelium, polyp tissues, and peripheral blood cells in AAA. In addition, a decrease in the expression of PGE2 receptors in inflammatory cells infiltrating the nasal mucosa was found in patients with AAA. One of the proofs of the protective effect of PGE2 is the fact that during a provocative test (PT) with ASA, inhalation of PGE2 helps to reduce bronchoconstriction and decrease the content of LTE4 in urine (which is usually higher in ABA than in atopic BA and in healthy individuals).

A characteristic feature of AAA is eosinophilic infiltration of the upper and lower respiratory tract. Hyperproduction of LT via the 5-LO pathway may be one of the important factors in the activation of eosinophils, on the surface of which receptors for various LT are expressed. In addition, another pathway of AK activation (15-LO) is known, which results in the additional formation of eosinophilic chemotactic factors

(EXA4, EXC4, EXD4, EXE4), the level of which is significantly increased in AAA [3]. Recently, the role of Staphylococcus aureus (S. aureus) superantigens in the pathogenesis of NERD has been intensively studied; a high degree of colonization of the respiratory tract mucosa by S. aureus has been detected. There is evidence that suppression of PGE2 receptor activity may be caused by S. aureus enterotoxin B. In addition, it was found that the level of serum immunoglobulin E (IgE) to enterotoxins A and B (SEA/SEB) is significantly higher in patients with AAA than in patients with atopic BA. Patients with high levels of IgE to SEA also have more pronounced bronchial hyperreactivity. IgE to S. aureus superantigens are detected not only in serum but also in the tissue of nasal polyps, the level of which correlates well with the activity of eosinophils. The presented facts indicate the involvement of a specific IgE response to S. aureus superantigens in the development of eosinophilic inflammation of the airways in AAA [4]. The hypothesis about the relationship between AAA and chronic viral infection deserves attention. According to this theory, supported by research results, the immune response to viruses leads to the appearance of specific cytotoxic lymphocytes. Their excessive activation is controlled by PGE2, and non-selective NSAIDs in patients with AAA block the production of PGE2, which results in an attack of cytotoxic lymphocytes on the cells of the respiratory tract infected with viruses. In the process of such reactions, lysosomal enzymes and inflammatory mediators are released, which leads to a persistent course and exacerbations of AAA [5].

NSAID-induced respiratory disease most often manifests itself in the form of the classic triad: asthma, HS to ASA/NSAIDs, polypous rhinosinusitis (PRS), but can also be observed in patients with asthma without PRS, with isolated PRS and, less often, in patients with non-polypous rhinosinusitis. Aspirin-induced asthma, as a rule, has a persistent course, is characterized by frequent exacerbations, including virus-induced ones, in some particularly severe cases, irreversible bronchial obstruction and steroid dependence can develop [1]. Rhinosinusitis in NERD is also characterized by a constant persistent course and infectious exacerbations. Nasal polyps are detected by endoscopy in 60% of patients with rhinosinusitis, and by computed tomography (CT) in 90% [2]. With long-term dynamic monitoring of the paranasal sinuses using CT, polyps are detected primarily in the sinuses, and only then in the nasal passages. As the disease progresses, all paranasal sinuses are involved (pansinusitis). Most patients with PRS complain of constant nasal congestion, hyposmia or anosmia, severe rhinorrhea with mucous or mucopurulent discharge, as well as facial pain and headache. Polyps usually recur after surgery if the patient does not receive glucocorticosteroid (GCS) therapy. NSAID-induced respiratory disease is more

common in women, with a ratio of 2:1 in men. The typical age of onset of the disease ranges from 20 to 40 years, but AAA is often a variant of late-onset BA. Sometimes the first signs of the disease appear in childhood. In rare cases, NERD is limited to PRS without the development of BA [3].

CONCLUSION

Despite the fact that ASA and NSAIDs are “classic” triggers of ABA, their elimination does not lead to remission of the disease, since the mechanisms of inflammation in this variant of BA are caused by the influence of many factors. Once they arise, diseases that form NERD continue throughout life, which requires constant anti-inflammatory therapy with GCS; some patients develop GCS dependence. Modern ICS and NGCS, combined drugs of ICS and long-acting β2-agonists, leukotriene receptor antagonists can improve the clinical condition and quality of life in a significant number of patients.

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