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REVIEW

Cofactors and comorbidities in patients with aspirin/NSAID hypersensitivity

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Abstract Hypersensitivity reactions to aspirin and other NSAIDs occur in individuals genetically predisposed and exhibit different clinical manifestations, especially respiratory, cutaneous, and generalised. Five different phenotypes define distinct clinical pictures: aspirin-exacerbated respiratory disease, aspirin/NSAID cutaneous disease, NSAID-induced urticaria, angio-oedema and anaphylaxis, single NSAID reactions, and delayed reactions. They are observed more frequently in middle-aged women, and in atopic individuals. While ASA/NSAID hypersensitivity shares comorbidities with asthma, chronic rhinosinusitis, nasal polyposis, chronic urticaria and angio-oedema, ASA and other NSAIDs can also be cofactors for other clinically relevant conditions, especially food-dependent exercise-induced anaphylaxis, angio-oedema induced by angiotensin-converting enzyme inhibitors, and oral mite anaphylaxis. Awareness on these relationships is required for the correct diagnosis, classification, and treatment of affected patients.

Introduction

Hypersensitivity reactions to aspirin (ASA) and other non-steroidal anti-inflammatory drugs (NSAIDs) are commonly observed in clinical practice, affecting 0.3–0.5% of the population.[1] Five clinical phenotypes have been described which include aspirin-exacerbated respiratory disease (AERD); aspirin/NSAID exacerbated cutaneous disease (AECD); aspirin/NSAID induced urticaria and angio-oedema; single NSAID-induced urticaria, angio-oedema and anaphylaxis; and delayed reactions (Table 1).[2]

Abbreviations: ADORA 3, adenosine receptor 3; ACEis, angiotensin-converting enzyme inhibitors; AE, angio-oedema; AECD, aspirin-exacerbated cutaneous disease; AERD, aspirin-exacerbated respiratory disease; ASA, aspirin; CU, chronic urticaria; FDEIA, food-dependent exercise-induced anaphylaxis; LTP, lipid transfer protein; NSAIDs, non-steroidal anti-inflammatory drugs; U/AE, Urticaria/angio-oedema.

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Table 1 Phenotypes of hypersensitivity reactions to NSAIDs.[a]

Type	Clinical picture	Comorbidities	Cross-reactivity with COX-1 inhibitors
Aspirin-exacerbated respiratory disease (AERD)	Asthma, rhinosinusitis, nasal polyposis	Asthma/rhinosinusitis	Yes
Aspirin/NSAID-exacerbated cutaneous disease	Urticaria and/or angio-oedema	Chronic spontaneous urticaria	Yes
NSAID-induced urticaria and angio-oedema	Urticaria and/or angio-oedema	None	Yes
Single NSAID-induced urticaria/angio-oedema or anaphylaxis	Urticaria/angioedema/anaphylaxis	None	No
Single NSAID-induced delayed reactions	Various (Fixed drug eruption, SJS, TEN)	None	No

SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.
[a] Modified from Ref.[2]

Although the clinical features of NSAID hypersensitivity have been extensively investigated, little information is available in the literature about possible cofactors contributing to those reactions and the comorbidities that should be taken into account when assessing a patient complaining of adverse reactions triggered by exposure to ASA and other NSAIDs.

In this paper we will discuss various factors that are associated with NSAID hypersensitivity, its relationship with atopy, patient's gender and age. Comorbidities and the association with food-dependent exercise-induced anaphylaxis and oral mite anaphylaxis will also be reviewed.

Cofactors and comorbidities in aspirin-exacerbated respiratory disease (AERD)

AERD affects 1–2% of the general population, 5–7% of asthmatics, is present in 2–25% of patients with severe asthma, and in 26–40% of patients who have the triad asthma-chronic rhinosinusitis-nasal polyposis. Also, about 15% of patients with nasal polyps are sensitive to aspirin. This condition usually begins as a flu-like syndrome between adolescence and 40 years of age, being more prevalent in females. Positive immediate hypersensitivity skin tests to inhalant allergens are present in one third to two thirds of AERD patients.

The initial picture is characterised by rhinitis and nasal congestion which is followed by chronic eosinophilic and hyperplastic pansinusitis, hyposmia, nasal polyposis and asthma (Fig. 1). Severity of asthma in these patients is moderate in 30% and severe in 50% of the cases. Exposure to aspirin or NSAIDs that inhibit cyclooxygenase-1 (COX-1) induces asthmatic exacerbations which can be life-threatening. Asthma observed in patients with AERD is frequently steroid-dependent.[3,4]

The mechanisms responsible for acute respiratory reactions to ASA/NSAIDs involve the inhibition of COX-1 isoenzyme, resulting in a decreased production of PGE2 and increased levels of cysteinyl-leukotrienes. On the other hand, the chronic eosinophilic inflammation of the upper and lower respiratory tract is mediated by an increased synthesis of cytokines with effects on eosinophils (IL-5, GM-CSF, RANTES, eotaxin). An increase of γ-interferon production by nasal polyp tissues has also been demonstrated.

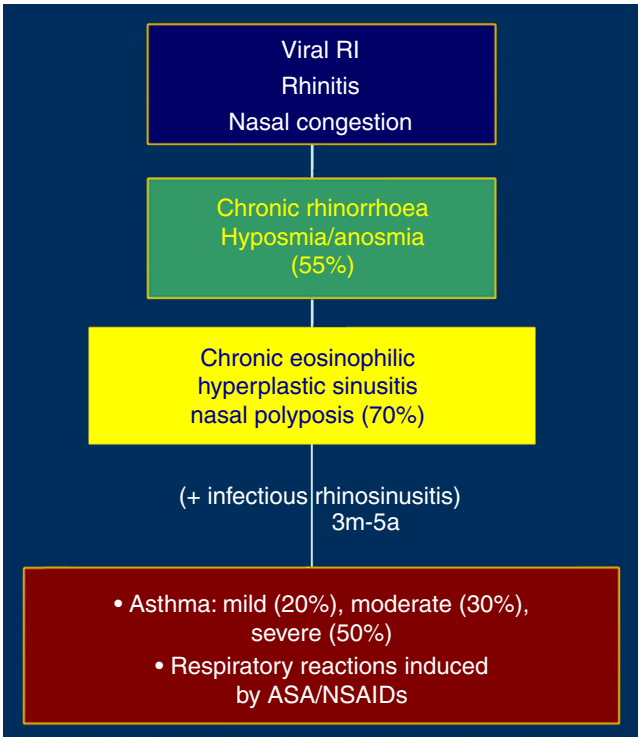

Figure 1 Natural history of aspirin-exacerbated respiratory disease (AERD).

The diagnosis of AERD is based on the medical history, nasal endoscopy, CT scan of paranasal sinuses, and aspirin challenge tests. For provocation tests the oral route constitutes the gold standard, although protocols for nasal and bronchial provocation tests are also utilised in many centres. The management of patients with AERD is summarised in Table 2.

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