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Review

The broken balance in aspirin hypersensitivity

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Abstract

Aspirin was introduced into medicine over a century ago and has become the most popular drug in the world. Although the first hypersensitivity reaction was described soon after aspirin had been marketed, only recently a phenomenon of cysteinyl leukotriene overproduction brought new insights on a balance between pro- and anti-inflammatory mediators derived from arachidonic acid. We describe the most common clinical presentations of aspirin hypersensitivity, i.e. aspirin-induced asthma, rhinosinusitis and aspirin-induced urticaria. We also present their biochemical background. Despite relatively high incidence of these reactions, aspirin hypersensitivity remains underdiagnosed worldwide.

Acute reactions of aspirin hypersensitivity are elicited via cyclooxygenase inhibition by non-steroid anti-inflammatory drugs. Coxibs, selective inhibitors of cyclooxygenase-2 isoenzyme, do not precipitate symptoms in susceptible patients. Though hypersensitivity correlates with cyclooxygenase-1 inhibition, diminished tissue expression was described only for cyclooxygenase-2.

Aspirin-induced asthma and aspirin-induced urticaria, in a substantial part of the patients, are driven by a release of mediators from activated mast cells. These cells in physiological conditions are under inhibitory control of prostaglandin E_2. The origin of aspirin hypersensitivity remains unknown, but accumulating data from genetic studies strongly suggest that environmental factor, possibly a common viral infection, can trigger the disease in susceptible subjects.

Keywords: Aspirin hypersensitivity; Cyclooxygenase; Non-steroid anti-inflammatory drug; Cysteinyl leukotriene; Lipoxin

Contents

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1. Historical note

The ancestry of aspirin (acetylsalicylic acid) goes back many thousands of years: salicylic acid, or salicylate, from which it is derived, is a constituent of several plants long used as medicaments (Vane and Botting, 1992; Brune and Hinz, 2004). Aspirin was introduced into medicine in 1899, and already three years later it was implicated as the cause of an anaphylactic reaction (Hirschberg, 1902; Settipane, 1990). Hirschberg in Poznañ, Poland presented the first case report of acute angioedema/urticaria occurring shortly after the ingestion of aspirin. This reaction subsided in 3 days, and the patient recovered completely.

Reports of anaphylactic reactions to aspirin followed soon. The acute bronchospasm was first reported by Cooke (1919), who noted that "symptoms begin as a rule from fifteen to twenty minutes after ingestion of 10 grains of the commercial drug (aspirin)". In 1920 Van der Veer described the first death from asphyxia due to aspirin (Van der Veer, 1920). The association of aspirin sensitivity, asthma and nasal polyps was reported by Widal et al. (1922). This clinical entity, later named "the aspirin triad", was popularized by studies of Samter and Beers (1968), who presented a perceptive description of the clinical course of this syndrome. In the 1970s the link between precipitation of asthmatic attacks and inhibition of cyclooxygenase by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) was described (Szczeklik et al., 1975, 1977).

Adverse reactions to aspirin and NSAIDs may have different clinical presentation and different pathogenesis. The two most common clinical presentations of aspirin hypersensitivity are: bronchial asthma and urticaria/angioedema.

2. Aspirin-induced asthma

Most people tolerate aspirin well, but asthmatics are an exception. In several patients with bronchial asthma, aspirin and other NSAIDs precipitate asthmatic attacks. In fact, by doing so, they uncover a specific clinical syndrome, characterized by aggressive and continuous inflammatory disease of the airways. The best description of this syndrome is probably aspirin-exacerbated respiratory disease (Szczeklik and Stevenson, 2003). However, most physicians refer to this condition as aspirin-induced asthma, and we use this term in this review.

2.1. Prevalence

The incidence of aspirin-induced asthma among adult asthmatics ranges from 3% to 21%. Three large population-based surveys from Finland, Poland, and Australia (Hedman et al., 1999; Kasper et al., 2003; Vally et al., 2002) were published recently. The prevalence of aspirin hypersensitivity in the general population ranged from 0.6% to 2.5%, and in asthmatics from 4.3% to 11 % (in Finland 8.8% of asthmatics, in Poland 4.3% asthmatics, in Australia 10.5%). Aspirin-induced asthma seems even more prevalent than previously suggested. In the last meta-analysis (Jenkins et al., 2004) the prevalence was the highest when determined by oral provocation testing (adults 21%, confidence interval 14% to 29%; children 5%, 0% to 14%) than by verbal history (adults 3%, 2–4%; children 2%, 1–3%).

Aspirin-induced asthma 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 (Szczeklik et al., 2000; Berges-Gimeno et al., 2002b). 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 (Sampson, 1999). Underdiagnosis of aspirin hypersensitivity is also the result of the lack of routine aspirin challenge testing of asthmatic patients.

2.2. Natural history and clinical characteristics

Aspirin-induced asthma progresses from the upper to the lower respiratory tract (Samter and Beers, 1968; Szczeklik and Stevenson, 2003; Szczeklik et al., 2000; Berges-Gimeno et al., 2002b). It is more frequent in women than in men, and is unusual in children, beginning in adulthood, on average at the age of 30 years. Rhinorrhea and nasal congestion are usually the first symptoms, subsequently complicated by nasal polyposis. 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 (Rosado et al., 2003) (Fig. 1).

Asthma, characterized by blood and nasal eosinophilia, runs a protracted course despite avoidance of analgesics. In at least half the patients, the course of asthma is severe (Szczeklik and Stevenson, 2003). In pan-European study, inhaled corticosteroids were used by 80% patients and oral corticosteroids by 39% to 51% (Szczeklik et al., 2000). In some patients, symptoms from the gastrointestinal (e.g., abdominal pain) or circulatory (retrosternal pain, shock) systems may follow aspirin challenge. Sporadic cases of myocardial ischemia after aspirin challenge were recently reported in aspirin-induced asthma patients and were associated with high cysteinyl leukotriene levels in urine (Szczeklik et al., 2002; Mattucci et al., 2002). Ocular complications are a frequent comorbidity in aspirin-induced asthma (Martin and Duvoisin, 2003).

A proportion of aspirin-induced asthma patients shows clinical manifestations and laboratory markers of autoimmunity (Szczeklik et al., 1995). Only occasionally do these symptoms prompt the patients to seek medical attention, either because they are of weak intensity or because their presence is overshadowed by major problems related to asthma. It is, therefore, interesting to note that autologous serum skin tests, suggestive of autoimmunity, were frequently observed in a group of patients with aspirin-sensitive urticaria (Asero et al., 2002).

2.3. Rhinosinusitis

Rhinorrhea and nasal congestion are usually the first symptoms of aspirin-induced asthma, and not infrequently the patient reports a typical virus cold before the onset of rhinitis.