

The aspirin disease

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Aspirin or acetylsalicylic acid (ASA) is still one of the most widely sold drugs in the world and its side effects are well known. Among these, hypersensitivity reactions represent one of the most frequently described since the first report of urticaria and angio-oedema by Hirshberg in 1902.¹

The hypersensitivity reactions to aspirin may be divided into two major categories²: type A characterised by respiratory symptoms (bronchial asthma, rhinitis) which account for about 15% of cases, and type B with urticaria and angio-oedema which occur in more than 75% of cases.³ A third category (type C) which includes any other peculiar clinical presentation (such as multiform erythema, fixed exanthema, Stevens-Johnson's syndrome, Lyell's syndrome) occurs in a small number of cases.

Females are more affected than males, except in childhood in which the asthmatic type A reactions are rare. A familial (and sometimes a personal) history of allergic disease is reported in about one third of cases.³ An extra-immunological ("pseudo-allergic") mechanism is involved in the pathogenesis of nearly all aspirin hypersensitivity reactions. The most accepted pathogenetic theory^{4,5} postulates that the cyclo-oxygenase (COX) block (COX-1 and COX-2) induced by aspirin leads to an increase in arachidonic acid metabolism by an alternative pathway represented by lipoxygenase. This in turn increases the synthesis of leukotrienes C₄, D₄, and E₄ which are able to exert a powerful bronchospastic action.^{6,7}

Aspirin (ASA) disease

An increasing number of reports concerning the existence of a relationship between bronchial asthma and the presence of nasal polyposis in the clinical picture of hypersensitivity reactions to aspirin has been accumulating in the literature since the late 1920s. The association of bronchial asthma and nasal polyposis in aspirin intolerant patients was first described by Widal in 1922⁸ and confirmed by several later reports.⁹⁻¹² This association is now so well established that in 1967 Samter and Beers¹³ defined the existence of the so called "aspirin disease" characterised by the association of aspirin intolerance, intrinsic bronchial asthma, and nasal polyposis (the aspirin triad).

The strict interrelationship between aspirin intolerance, bronchial asthma, and nasal polyposis has been confirmed by the statistical association between the prevalence rates of the different symptoms of the disease. Nasal polyposis occurs with a peak prevalence in the third and fourth decade. Its exact frequency in the general population is still unknown; the overall

prevalence probably exceeds 2%^{14,15} but this rises to 13% in subjects with intrinsic asthma,¹⁶ with a prevalence of 90% having been reported in patients with severe asthma.¹⁷ Such a figure is probably underestimated since much higher prevalence rates have been obtained in necroscopic studies.¹⁸ In more than one third of cases the disease is associated with intolerance to aspirin or to other non-steroidal anti-inflammatory drugs (NSAIDs)¹⁷; in as many as 20% of cases nasal polyposis is also associated with the presence of bronchial asthma and/or rhinitis, configuring the so-called aspirin triad or aspirin disease.¹³

Nasal polyposis has been reported to occur in as many as 31% of aspirin intolerant subjects.¹⁹ The overall prevalence of nasal polyps in aspirin intolerant subjects was reported to be 11.4% by our group,²⁰ but it reached 55% in subjects with type A aspirin intolerance, being therefore rare in those with types B (2.5%) and C (7.1%) intolerance.

Conversely, aspirin related asthma occurs in less than 0.2% of the general population while the presence of intrinsic bronchial asthma is reported in 40.2% of subjects with nasal polyposis and in 16.4% of aspirin intolerant subjects.³

Aspirin intolerance has been reported in 6-34% of asthmatic subjects,^{11,20,21} in 35-52% of subjects with polyps,^{3,22} and in as many as 64.5% of patients suffering from bronchial asthma and nasal polyps.³

A complete clinical picture of the aspirin triad is found in 7.6% of aspirin intolerant subjects, in 46.3% of type A aspirin intolerant subjects,^{3,10} and in 20% of patients with polyps.³

Bronchial asthma in aspirin disease is often severe and refractory to treatment.^{11,12,22,23} Aspirin disease is twice as common in woman as in men²² and affects mainly those in the 40-60 age group.

It is generally agreed that aspirin intolerance occurs after the onset of asthma in patients who had previously tolerated aspirin without difficulty. Aspirin sensitivity is often (68%) associated with intolerance to other NSAIDs.²⁴

Most patients with asthma who react to aspirin (89.8%) are already suffering from intrinsic asthma, while type B or C intolerance is not normally associated with specific symptoms except following administration of asthma.³

Methods

One hundred and fifty four consecutive subjects (65 males) aged 14-75 with nasal polyposis were studied as outpatients at the Department of Allergology of the Policlinico A Gemelli of Rome over a 10 year period from

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Table 1 Prevalence of nasal polyps in 420 patients with aspirin intolerance

Patients with polyps: 48 (11.4%); patients without polyps: 372 (88.6%)	
Aspirin intolerance	
Type A (n = 69)	38 with polyps (55%); 31 without polyps (45%)
Type B (n = 323)	8 with polyps (2.4%); 315 without polyps (97.6%)
Type C (n = 28)	2 with polyps (7.1%); 26 without polyps (92.9%)

Table 2 Prevalence of aspirin disease

Group	No. (%) of cases
Patients with aspirin intolerance (n = 420)	32 (7.6%)
Patients with aspirin intolerance type A (n = 69)	32 (46.3%)
Patients with nasal polyps (n = 154)	37 (24.0%)

1989 to 1998. All subjects underwent complete allergological evaluation together with measurements of serum specific IgE (RAST, Pharmacia) and serum eosinophil cationic protein (ECP) levels (UNICAP, Pharmacia). A nasal provocation test with lysine-acetylsalicylate was performed in all patients using the technique described previously.²⁵ A complete ear, nose and throat examination and computed tomographic (CT) scan of the maxillofacial region were also performed in all patients admitted to the follow up.

Results

NASAL POLYPS AND RHINITIS

Rhinitis was present in 117 of the 154 patients studied (76%).

NASAL POLYPS AND BRONCHIAL ASTHMA

Asthma occurred in 62 cases (40%), 87% of which were of the intrinsic type and 13% of the extrinsic type.

NASAL POLYPS AND ASPIRIN INTOLERANCE

Sensitivity to aspirin and other NSAIDs is found in a substantial number of patients with nasal polyps and occurred in 54 (35%) of the patients in our study. Of these, 74% reacted with rhinitis and asthma (type A sensitivity) while 26% developed urticaria and angioedema (type B sensitivity). In 68% of these 54 patients there was also sensitivity to other NSAIDs. On the other hand, in a group of 420 patients with aspirin intolerance nasal polyps occurred in 48 patients (11.4%), which increased to 55% in those who reacted to aspirin with asthma (type A sensitivity) (table 1).²⁰

ASTHMA AND ASPIRIN INTOLERANCE

In patients with aspirin intolerance, asthma was present in 16.4% of cases (69/420).³ The prevalence of aspirin sensitivity in patients with

Table 3 Serum ECP levels (µg/l) in normal subjects and patients with nasal polyps

	Normal values (<20 µg/l)	High values (>20 µg/l)	Mean (SE)	p value
Normal subjects (n = 99)	99	–	5.5 (0.31)	
Patients with polyps (n = 53)	23	– 30	11.27 (5.62) 67.5 (48.2)	<0.0001
Patients with aspirin disease (n = 8)	4	– 4	14.2 (6.5) 48.7 (12.4)	NS

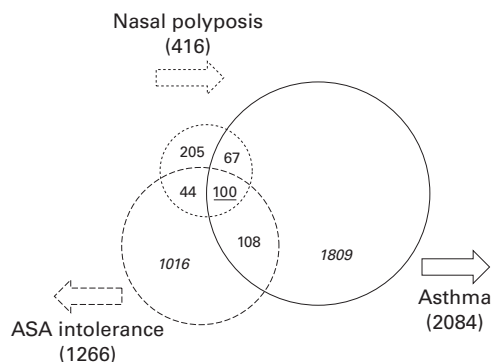


Figure 1 Statistical projection of aspirin (ASA) disease.

asthma varies, occurring in 6.3% of cases in our previous study.²⁰ Generally, an average of 10% is accepted in adult patients.²⁶

ASPIRIN DISEASE

In our previous studies^{3 20} aspirin disease occurred in 32 of 420 patients with aspirin intolerance (7.6%). This percentage increased to 46.3% (32/69) when only patients who reacted with asthma were included. In patients with nasal polyps aspirin disease occurred in 37 of 154 patients (24%; table 2). Based on these figures, we have created a mathematical model in which it is shown that, in order to obtain, for example, 100 cases of aspirin disease we need 416 patients with polyposis, 2084 with asthma, and 1266 with aspirin intolerance (fig 1).

Generally, rhinitis is the first symptom in the aspirin triad to appear, followed by asthma in 46.1% of cases, by nasal polyposis in 28.6% of cases, by aspirin intolerance in 14.2% of cases, and by other symptoms in 11.2%. The usual sequence for the temporal presentation of the symptoms of aspirin disease is: (1) chronic rhinitis, (2) bronchial asthma, (3) nasal polyposis or asthma intolerance.

SERUM ECP

Serum levels of ECP were detected in 53 patients with nasal polyps, 30 of whom (56.6%) had levels higher than 20 µg/l (mean (SE) 67.5 (48.2) µg/l) while 23 (44.4%) had levels lower than 20 µg/l (mean 11.27 (5.62) µg/l). This result was statistically significant (p<0.0001, one way analysis of variance) compared with 99 healthy subjects who all had serum ECP levels below 20 µg/l (mean 5.5 (0.31) µg/l). Four out of eight patients (50%) with aspirin disease had ECP levels above 20 µg/l (p<0.05, χ^2 test for contingency; p = NS, Fisher's exact test). These results confirm that, in patients with nasal polyps, there is higher chronic nasal inflammation with eosinophilic activation which is statistically significant (table 3).

Diagnosis

The diagnosis of aspirin disease is generally based on the clinical history. When aspirin disease is suspected but there is no history of possible aspirin sensitivity, an oral provocation test with aspirin should be undertaken.²⁷ This test is not free from risks and needs to be undertaken by a person experienced in medical

Table 4 NSAIDs which cross react with aspirin in respiratory reactions

(A) **Inhibitors of both COX-1 and COX-2** (there can also be reactions at the time of first administration of the drug with low doses): piroxicam, indomethacin, sulindac, tolmetin, ibuprofen, naproxen, ketoprofen, fenoprofen, meclofenamate, mefenamic acid, flurbiprofen, diflunisal, diclofenac, ketorolac, etodolac, nabumetone, aminopyrine

(B) **Poor inhibitors of COX-1 and COX-2** (a small percentage of patients with aspirin sensitivity cross reacts with high doses of these drugs): acetaminophen, salsalate

(C) **Relative inhibitors of COX-2 and minor inhibitors of COX-1** (there can be a cross reaction at high doses, but less serious): nimesulide, meloxicam

(D) **Selective inhibitors of COX-2** (there are no controlled clinical trials but these drugs should not cross react): celecoxib, rofecoxib

(E) **Non-inhibitors of COX-1 and COX-2** (these are analgesic drugs having an action on the central nervous system): tramadol, nefopam

Modified from Szezecklik *et al.*⁵

emergency procedures including resuscitation techniques. The bronchial²⁸ and nasal²⁵ provocation tests are less dangerous but are probably less sensitive. These tests can be used as alternatives to the oral provocation test in patients in whom it is suspected that the aspirin sensitivity is high.

Treatment

Aspirin disease has a number of aspects and each component of the syndrome requires specific treatment. Bronchial asthma is generally aggressive and patients are often steroid dependent. When nasal polyps cause chronic nasal obstruction in spite of medical treatment a surgical approach is recommended, but the rate of relapse after polypectomy ranges from 42% to 87% in 1–4 years.^{29–30} For such patients we use topical endonasal treatment with lysine-acetylsalicylate which is effective in reducing or preventing the relapse of nasal polyps after surgery. This approach is effective in both aspirin intolerant and aspirin tolerant patients.^{31–32}

The first approach to treating aspirin intolerance is to stop these patients using aspirin and other NSAIDs with similar activity (table 4). As alternatives they can be given nimesulide or acetaminophen (paracetamol) for fever, and nimesulide, acetaminophen or tramadol for pain.³³ A tolerance test under medical supervision is useful because there is the possibility of adverse reactions (asthma, urticaria) in 5–7% of these cases. Oral desensitisation to aspirin is also useful to prevent the recurrence of nasal polyps and to improve asthma in aspirin intolerant patients.^{34–35} Several recent studies have suggested that leukotriene antagonists and synthase inhibitors may be useful.^{36–40}

Conclusions

- Aspirin disease may be severe.
- The use of NSAIDs in patients with nasal polyps should be avoided.
- The presence of nasal polyps in aspirin intolerant patients with asthma should be investigated by computed tomographic scanning and rhinoscopy.
- Endonasal treatment with lysine-acetylsalicylate is useful in preventing recurrence of nasal polyps if used in association with traditional medical and surgical approaches.
- Long term treatment with oral aspirin (desensitisation) may improve asthma and nasal polyposis.

- Leukotriene antagonists may have a role in reducing the intensity of the severe crises of asthma caused by aspirin and other NSAIDs.

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