

Aspirin and subtypes of asthma: Risk factor analysis

Constantine J. Falliers, M.D. *Denver, Colo.*

Among 1,298 children 6 to 16 years old, initially observed in a residential center for chronic asthma and subsequently followed over a 14 year period, 25 (1.9 per cent) exhibited adverse reactions (urticaria, angioedema, asthma, hypotension) to ordinary doses of aspirin. A survey of individual clinical characteristics of these patients indicated that the small group with acetylsalicylic acid (ASA) intolerance differed from the rest of the asthmatic population in several respects. Onset of asthma in the former was sudden and later (median 11 years) vs. early (median 2 years) for the rest of the patients. Girls outnumbered boys (M:F ratio 0.8 vs. 2.6); eczema was noted only in one case (4 per cent vs. 46 per cent), and personal as well as family histories for Type I, reagin-mediated allergic reactions, were mostly negative. Nasal polyps were noted in 27 per cent of the ASA reactors but in none of the other patients. On the basis of the observed concurrence, the probability (risk) of ASA reactions, atopic eczema, nasal polyposis, and a heightened familial incidence of asthma were estimated for subsets of asthmatic patients. The complexity inherent in studies of clinical phenomena with variable age of onset is recognized.

Acetylsalicylic acid (ASA, aspirin) is a widely used analgesic, antipyretic, and anti-inflammatory drug. Controlled clinical trials¹ and authoritative evaluations² provide evidence that aspirin equals or surpasses the effect of other mild analgesics. A variety of preparations containing ASA (Table I) are available and usually are taken without prescription and without the patient being aware of the aspirin content of these compounds.

Adverse reactions, resembling anaphylaxis, were reported soon after the introduction of aspirin in therapeutics. Recent surveys have summarized the clinical characteristics of these reactions³⁻⁷ and have debated the question of whether or not these are due to allergic processes.^{5, 8, 9} Individuals suffering from respiratory allergy, namely asthma, are considered exceptionally prone to develop untoward reactions to ASA.^{4, 5, 7} The incidence of such reactions has been reported as varying, from 2.3 per cent in an unselected population of asthmatic patients,⁴ up to 20 per cent among adult patients with severe asthma.¹⁰ Cross-sensitivity with other analgesic drugs and also with common food and drug additives has been reported.^{5, 11, 12} No detailed statistics are available on the incidence of ASA reactions among children, with or without allergic problems, and no effort has been made, in the pediatric literature at least, to correlate the occurrence of ASA reactions to specific disease patterns. Following initial observations, which established the fact that untoward reactions to ASA do occur in childhood, the present study was undertaken in order to (1) ascer-

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TABLE I. Common preparations containing acetylsalicylic acid (ASA)

Alka-Seltzer	Edrisal
Anacin	Empirin
Anahist	Excedrin
APC compound	Fiorinal
Ascriptin	Midol
Aspergum	Percodan
Aspirin	Phenergan compound
Bufferin	Pyrroxate
Cope	Sine-off
Coricidin	Trigesic
Darvon compound	Vanquish
Dristan	Zactirin

TABLE II. Reactions* to aspirin and to penicillin reported by the families of 623 asthmatic children

	Aspirin	Penicillin
Mother	2	61
Father	1	35
Maternal grandmother	3	12
Maternal grandfather	0	1
Paternal grandmother	0	5
Paternal grandfather	0	6
Brothers	2	38
Sisters	1	24

*Generally described as "rashes."

tain the incidence of ASA reactions (hypersensitivity or intolerance) in a population of children with severe persistent asthma and (2) determine whether, on the basis of clinical and other criteria, subtypes of asthma could be defined with high- or low-risk factors for ASA reactions.

METHOD

Demographic and clinical information was obtained on 1,298 children (360 girls, 938 boys) 6 to 16 years of age, who were observed during a 14 year period. The data-base consisted of the medical records on each patient before, during, and, in most cases, after participation in the residential treatment program of CARH in Denver. The method for the selection of these patients, their place of origin, the nature of the treatment program, and the results obtained have been reported previously.¹³

All information for this survey was validated by collecting data from at least two sources (usually the parents and the referring physician) and by repeated personal interviews subsequently. The patients, their parents, and their referring physician were asked specifically to report and describe adverse reactions to aspirin, other salicylates, other analgesics and antipyretics, with specific mention of generic and proprietary names of the most common ones. Reactions to other drugs were also recorded. In this population of patients there was an obvious tendency to over-report (false positive) drug reactions. Therefore, every possible effort was made to obtain a description of ASA reactions from a reliable source (generally a physician), including observations on the presence, duration, and severity of urticaria, angioedema, dyspnea, wheezing, hypotension, gastrointestinal disturbances, and other relevant symptoms and signs. The review did not detect any false negative cases, where lack of information did not imply absence of adverse reactions.

No effort was made to confirm or to rule out ASA intolerance by experimental administration of aspirin to our patients or to their relatives.

Prospective information was obtained with questionnaires sent to all patients discharged

TABLE III. Characteristics of asthmatic patients with and without aspirin intolerance

Clinical criteria	Confirmed ASA reactions	No ASA reactions
Onset of asthma	Late (median: 11 yr.)	Early (median: 2 yr.)
Atopic eczema	Rare (4%)	Common (42%)
Allergic sensitivities	Infrequent (16%)	Prevalent (80%)
Nasal polyps	Common (27%)	None noted
Sex ratio (M/F)	0.78	2.67
Response to treatment	Poor	Variable
Asthma-allergy in family	Infrequent	300%-500% of expected
ASA reactions in relatives	Rare	Rare

over the past 14 years. The median follow-up period was 3.7 years. All relevant observations were recorded manually, and, subsequently, selected demographic and clinical data were processed by the IBM 1130 computer system.

RESULTS

A tabulation of reactions to aspirin and penicillin, reported by the families of our patients over the second 7 year period of this investigation (Table II), shows the data in this survey. The rather striking incidence of reported reactions to penicillin (which further scrutiny could not confirm in most instances) makes the negative histories of most families regarding aspirin seem noteworthy.

Our survey identified 25 cases of ASA intolerance, showing an incidence of 1.92 per cent among these patients. This is slightly lower than the figure of 2.3 per cent reported for an unselected population of asthmatic patients⁴ and ten times lower than the incidence reported in a population of adults institutionalized for severe chronic asthma.¹⁰

Initial tabulation of various characteristics of the patients with confirmed ASA reactions indicated that the phenomenon of intolerance to aspirin was not a random occurrence within the total population of children suffering from chronic asthma. The median age at the onset of asthma for the children who were not intolerant to ASA was 2 years (Table III). It was 11 years for the patients with confirmed ASA intolerance. Atopic eczema was present, or had been present in the past, in 42 per cent of the children with no ASA intolerance. It affected only one (4 per cent) of the patients in the ASA-sensitive group. Immediate-type allergic skin reactions were prevalent in the large group of ASA-negative patients but were noted infrequently among the 25 patients who had a positive history of ASA reactions. Nasal polyps were not noted in any of the cases with no aspirin intolerance, but they were commonly detected in individuals who had experienced adverse reactions to aspirin. Boys outnumbered girls two and one-half times in the young asthmatic population not sensitive to ASA, while the reverse was true (male:female ratio 0.8) among the patients with late onset of asthma and ASA intolerance.

A family history of allergy, specifically asthma, atopic eczema, and rhinitis, was commonly reported by patients with a negative history for ASA intolerance. In 16 per cent of these patients (i.e., nearly 5 times the expected random risk), one or both parents gave a history of asthma. Atopic diseases in general, asthma, rhinitis, or eczema, were reported by 63 per cent of the parents

TABLE IV. Matrix of variables related to asthma and ASA reactions

	Onset of Asthma			Eczema	Rhinitis
	Under 3 yr.	3-9 yr.	9-15 yr.		
Onset of asthma					
Age 0.01-2.99 yr.	998	—*	—	499	221
Age 3.00-8.99 yr.	—	238	—	20	45
Age 9.00-14.5 yr.	—	—	62	2	46
Atopic eczema	499	20	2	52	168
Rhinitis	221	45	46	168	302
Nasal polyps	0	0	9	1	9
Allergy tests					
Positive	841	193	13	—	—
Negative	157	45	49	—	—
ASA reactions	4	3	18	3	20
Sex					
Female	268	59	33	176	111
Male	730	179	29	345	191
Family history					
Asthma	135	56	5	96	68
Asthma/eczema	501	108	9	202	102
ASA reactions	1	0	1	1	1

Mother, father, siblings, excluding adopted Sc-N: 1,261.

*Noncomputed, or nonapplicable data.

TABLE V. Risk factor analysis (Probability estimated on a 0% to 100% scale)

Primary condition*	Probability				
	Family history of asthma	Atopic eczema	Nasal polyps	Positive skin tests	ASA reactions
Asthma—no other information	15	41	0.6	79	1.9
Asthma, early onset (1-3 yr.)	16	50	0	84	0.004
Asthma, late onset (9-14 yr.)	8	3.2	14.5	21	29
Asthma and eczema	18	100	0.001	85	0.005
Asthma and polyps	30	11	100	30	78
Asthma and ASA reactions	12	12	36	20	100
Estimated incidence in general	3.6	12	?	10 (?)	< 0.001 (?)

*As defined.

and siblings of these patients. On the other hand, among the 25 patients with ASA intolerance, 3 (12 per cent) had parents or siblings with a history of asthma, and a total of 7 (28 per cent) reported asthma or eczema or rhinitis in their immediate families. A family history of ASA intolerance was noted (without experimental confirmation) in a total of 6 cases, 5 of whom were relatives of the ASA-negative majority group of children.

The clinical course of the patients during the period of observation also showed differences. While between 46 per cent (in the early years) and 11 per cent (in recent years) of the ASA-negative patients responded well to the institutional treatment program,¹³ only one of the ASA-sensitive group did well, without much medication. Generally, continuous bronchodilator and corticosteroid therapy was required for adequate control of asthma in these patients.

Polyps	Allergy skin tests		ASA reactions	Sex		Family history		
	Positive (+)	Neg. (—)		Male	Female	Asthma	Asthma and eczema	ASA reactions
0	841	157	4	268	730	135	501	1
0	193	45	3	59	179	56	108	0
9	13	49	18	33	29	5	9	1
1	—	—	3	176	345	96	202	1
9	—	—	20	111	191	68	102	1
9	—	—	7	6	3	3	5	0
—	1,044	—	4	288	756	—	—	—
—	—	254	21	472	182	—	—	—
7	4	21	25	14	11	3	7	0
6	288	72	14	360	—	68	—	—
3	756	182	11	—	938	—	—	—
3	—	—	3	2	1	196	—	—
5	—	—	7	5	2	—	618	—
0	—	—	0	0	0	—	—	2

Antibiotics were also prescribed frequently for recurrent respiratory infections, thought to be, at least partly, of bacterial origin.

Computer outputs listed the actual combinations of two or more of the clinical characteristics investigated. The list contained both descriptive and dichotomous ("yes-no") data (Table IV). Attention was focused selectively on certain fairly evident clusters of clinical phenomena. Statistically significant correlations were noted among several of the variables examined. ASA intolerance was positively correlated with a late onset of asthma, with nasal polyps, and with the sex being female. It was negatively correlated with the presence or a past history of atopic eczema and with reagin-mediated wheal and erythema skin reactions. A family history of atopic disease, including asthma, showed a trend of being negative when a history of ASA intolerance was positive. Table V expresses, on a 0 to 100 per cent scale, the probability of the occurrence of a specific condition, when one or more other clinical disorders are known to exist. For instance, it was estimated that a person with an early onset of atopic asthma, with a positive family history and with reagin-mediated allergic sensitivity, has a near-zero risk for ASA intolerance. On the other hand, a patient with asthma of late onset, near or during adolescence, has a high probability of reacting adversely to aspirin and having nasal polyps, while his or her chances of having, or having had, eczema are very low.

DISCUSSION

Recent reviews have demonstrated the concurrence of asthma with aspirin intolerance.³⁻⁷ The present study offers evidence that the asthma associated with ASA intolerance is different from atopic asthma, which is the type more commonly seen in childhood. This distinction is evident in several publications. The cases described by Samter and Beers,^{5, 6} and Giraldo, Blumenthal, and

Spink,⁷ reviewed in this report, were characterized by sudden late onset of persistent asthma, immediate anaphylactic-type reactions to ASA, nasal polyps, and an absence of atopic disease in the personal and in the family histories ("intrinsic" asthma).

Serious adverse reactions to ordinary therapeutic doses of aspirin obviously do not occur at random among asthmatic patients. Specifically in pediatrics, where atopy is commonly part of the clinical syndrome of asthma, the lack of personal and family antecedents among ASA-sensitive patients seems impressive. Another important differentiating factor is the patient's sex. While the prevalence of asthma in the first two decades of life is twice, or two and one-half times higher in males than in females, the reverse seem true among ASA-sensitive asthmatics. A striking example can be found in Giraldo, Blumenthal, and Spink's report, which included 7 patients under 20 years of age with asthma and ASA intolerance. The fact that they were *all* female cannot easily be attributed to chance alone.

A similar distinction applies to nasal polyps. As Caplin, Haynes, and Spahn¹⁴ reported, nasal polyposis is *not* part of the atopic syndrome, which consists of the primary triad: asthma, rhinitis, and eczema. However, polyps do seem to be associated with the asthma-ASA intolerance syndrome.

Asthmatic patients sensitive to ASA are not atopic except coincidentally. In addition to negative skin tests and a negative family history for asthma, the absence of eczema and the presence of polyps strengthen our differentiation. With the exception of one recent report,¹⁵ there is no evidence that ASA intolerance is genetically transmitted.

As far as the manifestations and the severity of asthma itself are concerned, Samter and Beers^{5, 6} comment on the "surprisingly low dose of corticosteroids" required for the control of asthma in their ASA-intolerant patient. One could reverse the argument and comment that what seems surprising is that most asthmatics with ASA intolerance require virtually continuous corticosteroid therapy. The use of corticosteroids for atopic asthma is the exception, not the rule. When steroids are needed, even in high doses, it is for short intervals of time. For the nonatopic, "intrinsic" asthma of late onset, by contrast, corticosteroids are necessary indefinitely to reduce its morbidity and mortality.^{16, 17}

There is no known immunologic or metabolic dysfunction responsible for ASA reactions, or indeed for nonatopic, late-onset asthma in general. The likelihood that ASA-induced asthma and possibly other nonspecific bronchoconstrictive reactions result from an antidromic axon reflex was imaginatively and, it seems, convincingly postulated by Samter and Beers.^{5, 6} Irrespective of etiologic considerations, clinical data on aspirin-induced bronchial obstruction contribute to the understanding of asthma by making possible a more precise taxonomy of asthma and the recognition of clinical entities with different pathogenesis and prognosis. The postulated conversion of chemoreceptor responses from antagonist to agonist⁵ provides an explanation for common clinical observations and may "open the door" for further research on how aspirin and the aspirin-prostaglandin relationship¹⁸ might be significant elements in the pathogenesis and also, possibly, in the treatment of asthma.

Let us also be reminded that when considering disorders of variable age of onset, we must estimate the risk by introducing corrective computations¹⁰ or by extending our observations during our subjects' entire lifetime. The identification of clinical subtypes and of risk categories may stimulate future investigations to carry this task eventually to completion.

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