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Aspirin intolerance

I. Frequency in an allergic population

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The frequency of intolerance to aspirin in a total population of asthma and/or rhinitis was 89 out of 3,781 or 2.4 per cent. In the asthmatic group, the frequency was 4.3 per cent. Those asthmatics with negative allergy skin tests had significantly more aspirin intolerance (6.8 per cent) than did those with positive skin tests (3.5 per cent) ($p < 0.01$). The frequency of intolerance to aspirin increased with advancing years (1.4 per cent for those under 20 years of age compared to 6.3 per cent for those 50 years of age or over). In those patients with rhinitis alone it was 0.7 per cent, a significantly lower value than found in those who had both asthma and rhinitis, 4.5 per cent ($p < 0.001$). Of the 89 patients, 59 or 66 per cent reported bronchospasm, 29 or 33 per cent reported urticaria, and 9 or 10 per cent reported rhinitis after ingestion of aspirin. Bronchospasm was the primary manifestation of aspirin intolerance in patients with known asthma, while the manifestations of urticaria were the predominant symptom of patients with known rhinitis (alone). It is important to compare the characteristics of an aspirin-intolerant group to that of the population from which it is selected.

Adverse reactions to acetylsalicylic acid, aspirin, have been known for over 70 years.¹ A review of the literature reveals a definite need for population studies to determine the frequency and nature of intolerance to this drug. In this report, we have attempted to evaluate the frequency and characteristics found in a selected group of patients intolerant to aspirin with the characteristics found in a given population of allergic subjects from which the former group was derived.

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TABLE I. Frequency of aspirin intolerance in various age groups of asthmatic patients

Age when first seen (years)	No. with asthma	No. with ASA intolerance	% *	No. with broncho-spasm	% *	No. with urticaria/angioedema	% †
10-19	358	5	1.4	3	0.8	2	0.6
20-29	351	13	3.7	6	1.7	6	1.7
30-39	342	12	3.5	11	3.2	3	0.9
40-49	357	24	6.7	18	5.0	7	2.0
50 and over	367	22	6.0	17	4.6	2	0.5
Total	1,775	76	4.3	55	3.1	20	1.1

*The trend of progressive differences by decades is statistically significant ($p < 0.01$).

†The trend of differences is not statistically significant. Included are 3 patients who manifested both bronchospasm and urticaria. Four patients with aspirin intolerance manifested solely by rhinorrhea are not included in this table.

MATERIAL AND METHODS

The records of private patients of an allergist practicing in Providence, Rhode Island, were reviewed. This was facilitated by a program of coding pertinent details of each record onto McBee Keysort cards, which had been in use for many years to provide quick and accurate retrieval of information. The few records of children first seen under the age of 10 years were excluded. A diagnosis of asthma or rhinitis was found in 3,781 records, and these cases formed the population of this study. All patients had been tested by the scratch technique to a battery of inhalant allergens.* When the scratch test was negative for a particular allergen that was suspected by history, the intracutaneous test was also done. Allergens included tree, grass, and ragweed pollens, animal danders, and selected molds. A positive reaction had to be definitely larger than the control, and all questionable reactions were considered as negative tests. The cases were sorted into those with a diagnosis of asthma alone (1,133); those with only rhinitis, seasonal or nonseasonal (2,006); and those with both of these conditions (642). The records for each diagnosis were subdivided into those patients who had positive allergy skin tests to one or more pollen, dander, or mold and those with negative reactions to those antigens. Cases of infectious rhinitis were excluded from this study. Vasomotor rhinitis was classified with those cases of rhinitis with negative skin tests. A diagnosis of asthma was accepted if symptoms consisted of clinically reversible signs of wheezing, shortness of breath, and cough on a recurrent basis, not due to any other organic disease. A diagnosis of rhinitis was accepted if symptoms consisted of repeated nasal stuffiness, rhinorrhea, and frequent sneezing on a seasonal or nonseasonal basis. The records were then divided according to sex, and further arranged by decades according to the age when first seen. Those patients 50 years of age and over were classified into one group.

All patients had been routinely questioned for any symptom of possible intolerance to aspirin, and their answers had been specifically included on the Keysort cards. Since aspirin is in such common use, it is assumed that all patients had at one time ingested it. Acute wheezing, rhinorrhea, sneezing, urticaria, angioedema, or symptoms of shock occurring within 2 hours after ingestion were our criteria for intolerance to aspirin. There were 89 records in which one or more of these symptoms occurred. There was no instance of shock. Angioedema was included in the category of urticaria. These 89 cases were carefully scrutinized as to the family history of allergy, the presence of nasal polyps, and the type of response to aspirin ingestion.

RESULTS

Out of 3,781 patients, 1,133 or 30 per cent had asthma alone, 642 or 17 per cent had both asthma and allergic rhinitis, and 2,006 or 53 per cent had allergic

*The standard scratch tests as purchased by Hollistier-Stier Laboratories.

TABLE II. Frequency of aspirin intolerance in rhinitis alone compared to rhinitis with asthma

Sex	Rhinitis alone			Rhinitis and asthma		
	Number	Aspirin intolerance	%	Number	Intolerance	%
Male	868	6	0.7	280	13	4.6
Female	1,138	7	0.6	362	16	4.3
Total	2,006	13	0.7*	642	29	4.5*

*This difference is statistically significant ($p < 0.001$).

rhinitis alone. Of the total population 44 per cent were males and 56 per cent were females, and this sex ratio was approximately similar in each of the preceding categories. These 3,781 patients were further classified into age when first seen. The age range was from 10 to over 50 years of age with a slight predominance in the younger age groups. There were 24.5 per cent in the 10 to 19 year age group, 23.3 per cent in the 20 to 29 year age group, 20.6 per cent in the 30 to 39 year age group, 17.1 per cent in the 40 to 49 year age group, and 15 per cent were 50 years of age or older.

The frequency of aspirin intolerance in our total population was 89 out of 3,781 or 2.4 per cent. In the asthmatic group of 1,775 cases the frequency of aspirin sensitivity was 4.3 per cent. Those asthmatics with negative skin tests to inhalant allergens, intrinsic asthma, had significantly ($p < 0.01$) more aspirin intolerance (29 out of 427 or 6.8 per cent) than asthmatics with positive skin tests, extrinsic asthma (47 out of 1,348 or 3.5 per cent). A greater frequency of intolerance to aspirin in intrinsic asthma was noted in all age groups, and this frequency of intolerance appeared to increase with advancing years. For example, those individuals under 20 years of age had a frequency of 1.4 per cent, while those 50 years of age or older had a frequency of 6.0 per cent (Table I).

The frequency of aspirin sensitivity in patients with rhinitis (alone) was 13 out of 2,006 or 0.7 per cent. There was essentially no difference in the rhinitis with positive allergy skin tests compared to the rhinitis with negative allergy skin tests. However, when the frequency of aspirin intolerance in patients with rhinitis alone (0.7 per cent) was compared to the frequency found in patients with rhinitis and asthma (29 out of 642 or 4.5 per cent), this difference became highly significant ($p < 0.001$) (Table II). The two manifestations of aspirin intolerance, bronchospasm and urticaria, were found in different frequencies in aspirin-intolerant patients with known asthma compared to those with known rhinitis alone (Table III). The manifestation of urticaria was found to be in greater proportion in those aspirin-intolerant patients with known rhinitis alone. The manifestation of bronchospasm in aspirin-intolerant patients with known asthma was statistically greater ($p < 0.01$) than the manifestation of urticaria in these same patients. In addition, the frequency of bronchospasm in aspirin-intolerant patients with intrinsic asthma was greater than in those with extrinsic asthma ($p < 0.01$). However, the frequency of urticaria was not significantly different in the extrinsic compared to the intrinsic asthmatic. The frequency of one or more positive skin tests was greater in those intolerant

TABLE III. Frequency of bronchospasm and urticaria as manifestations of aspirin intolerance in asthmatic patients

	Total No.	No. with bronchospasm	%	p value	No. with urticaria/angioedema	%	p value
Extrinsic asthma (positive skin tests)	1,348	30	2.2	< 0.01	17	1.3	N.S.
Intrinsic asthma (negative skin tests)	427	25	5.9		3	0.7	
Total asthma	1,775	55	3.1*	< 0.01	20	1.1*	< 0.01
Rhinitis alone	2,006	4	0.2†		8	0.4†	

N. S. = not significant.

Three cases who reacted with both bronchospasm and urticaria are included. Four cases of aspirin intolerance manifested solely by rhinorrhea are not included in this table.

*The difference between the number of asthmatics whose symptoms of aspirin intolerance were manifested by bronchospasm (3.1%) as compared to those whose symptoms were manifested by urticaria (1.1%) is statistically significant ($p < 0.01$).

†Not significantly different.

patients who on ingestion of aspirin manifested only urticaria (22 of 25 or 88 per cent) than in those who manifested only acute bronchospasm (31 of 55 or 56.4 per cent) ($p < 0.01$).

In known asthmatics, the increased frequency of intolerance to aspirin with advancing age appeared to be significantly influenced by the symptom of bronchospasm ($p < 0.01$) rather than by that of urticaria (Table I). There was no significant sex difference found in any of our categories. Of the 89 patients with aspirin sensitivity, the frequency of symptoms that occurred after aspirin ingestion was as follows: bronchospasm, 66 per cent; urticaria or angioedema, 33 per cent; and severe rhinitis, 10 per cent. There was a history of multiple drug allergy in 18 per cent and also a tartrazine sensitivity in 2 per cent. Other characteristics found in these patients with aspirin sensitivity are listed in Table IV. Nasal polyps were noted either at the physical examination or by ENT consultation.

DISCUSSION

Epidemiological surveys should include two types of detailed examinations. The first examination should be the characteristics of the selected or afflicted group and the second examination must include a search for these same characteristics in the population from which the group was selected. In this manner a particular characteristic found in the selected group is evaluated for its uniqueness in the population.

In our population of 3,781 allergic patients, 89 had aspirin intolerance and presented the following characteristics: a predominance of females; a relatively older age group; a positive family history of asthma or allergic rhinitis in 51 per cent; and one or more positive skin tests to pollens, animal danders, or molds in 65 per cent. Most studies showed similar findings in those with aspirin

TABLE IV. Eighty-nine patients with aspirin intolerance

Clinical data	Number	%
Males	35	39
Females	54	61
Positive allergy skin tests	58	65
Nasal polyps	32	36
Positive family history of atopy	45	51
Symptoms of aspirin intolerance*		
Bronchospasm	59	66
Urticaria/angioedema	29	33
Rhinitis	9	10

*Includes patients whose symptoms of aspirin intolerance involve more than one of these categories.

intolerance but their results were not evaluated and compared with the total population from which the aspirin-intolerant group was chosen.

In our total allergic population of 3,781, a predominance of females exists (56 per cent). The 61 per cent of females found in our intolerant group may actually be reflecting this disproportionate sex ratio of the total allergic population. There was no statistically significant sex difference found in any of our categories. Most past studies²⁻⁶ showing a predominance of females in individuals with aspirin intolerance failed to show the sex ratio of the total population from which the intolerant group was selected.

The frequency of aspirin intolerance in a population is also dependent on the characteristics of that population. Factors that may affect this frequency are as follows: The number and type of asthma and allergic rhinitis, the age group of the population, and method of study. Our data indicates that a population consisting largely of patients with allergic rhinitis or of a younger age group will have a lower frequency of aspirin intolerance.

Our frequency of intolerance in our asthmatic population was 4.3 per cent. This frequency is similar to other studies done on asthmatic individuals. Walton and Randle⁴ reported a frequency of intolerance to be 3.2 per cent in 2,580 asthmatic patients. Although they stated that their intolerant group was equally divided between extrinsic and intrinsic asthma, they did not report what percentage of their total asthmatic population had extrinsic or intrinsic asthma. Pearson¹⁰ reported a frequency of aspirin intolerance to be 2.3 per cent of 1,205 asthmatics. Although he demonstrated that this intolerance occurred more frequently in an older age group, as was noted in our study, he did not report how many of his asthmatics had intrinsic or extrinsic asthma. In their survey Gardner and Blanton¹¹ asked 95 allergists, "How many cases of aspirin sensitivity have you encountered and what per cent does this represent of all the allergic patients you have seen?" Their estimate revealed a frequency of 0.2 per cent. McDonald, Mathison, and Stevenson⁹ reported a frequency of 5 per cent in 282 asthmatic patients. However, after challenging certain selected asthmatics, their frequency of aspirin intolerance increased to 8 per cent.

Past reports of a positive family history of atopy in those individuals with aspirin intolerance range from 50 per cent, reported by Samter and Beers,^{2, 3}

to 65 per cent by Walton and Randle.⁴ If the total population from which the aspirin-intolerant group was selected is essentially an atopic population, a positive family history of over 50 per cent is to be expected.⁷ Therefore, the increased frequency of a positive family history of allergy may not be a unique property of intolerance to aspirin.

A positive allergy skin test was found in 65 per cent of our aspirin-intolerant group, and this increased frequency probably reflects the general characteristics of the total population^{7, 8} from which our group was chosen. Other investigations^{4, 5, 9, 10} on aspirin-intolerant patients who were selected from an allergic population also have showed high frequencies of positive allergy skin tests. Samter and Beers^{2, 3} selected 183 patients with aspirin intolerance not from an allergic population but from the medical wards of a hospital. Their data proved to be dramatically different in that only 10 per cent of their 182 patients with intolerance had positive allergy skin tests to seasonal and environmental inhalant allergens. This demonstrates that positive allergy skin tests may not be a characteristic of aspirin intolerance. Our data also supports this finding by showing that significantly more intrinsic than extrinsic asthmatics have an intolerance to aspirin.

Similar to other reports,⁴⁻⁶ the most common manifestations of aspirin intolerance in our patients were bronchospasm (66 per cent), urticaria and angioedema (33 per cent), and rhinitis (10 per cent). Our data also agrees with other studies^{3, 5, 6, 9, 10} in that a significant number of our aspirin-intolerant patients had nasal polyposis (36 per cent). We were not able to judge the severity of asthmatic symptoms in our aspirin-intolerant patients in relation to the severity of asthma in our total population.

The fact that bronchospasm is the predominant symptom of aspirin intolerance in patients with known asthma compared to those aspirin-intolerant patients with known rhinitis alone may demonstrate that aspirin may somehow enhance or interact with a defect already present in selected asthmatic patients. This enhancement of an existing defect may account for the greater frequency of aspirin intolerance in the asthmatic compared to the patient with rhinitis alone. Patients with rhinitis alone do not have an increased frequency of bronchospasm, but when the primary diagnosis of rhinitis and asthma coexists in the same patient, the symptom of bronchospasm as a manifestation of intolerance again predominates.

The frequency of positive skin tests in those patients whose aspirin intolerance is manifested by urticaria/angioedema is greater (88 per cent) than in those whose manifestation is bronchospasm (56 per cent) ($p < 0.01$). This difference together with our other data presented may imply that a reaction of urticaria/angioedema may be related to atopy while one of acute bronchospasm is not.

The frequency of multiple drug allergies in our aspirin-intolerant group (18 per cent) is similar to that reported by Samter and Beers (22 per cent).^{2, 3} Our frequency of intolerance to tartrazine was only 2 per cent of the group that was intolerant to aspirin. However, the association of intolerance to aspirin and

to tartrazine has been reported in the literature,^{12, 13} and if all our aspirin-intolerant patients were challenged with tartrazine, the frequency of associated tartrazine intolerance might be increased.

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