Aspirin intolerance. III. Subtypes, familial occurrence, and cross-reactivity with tartrazine

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Evidence has been presented supporting the hypothesis that at least 2 different types of mechanisms may be involved in aspirin intolerance, one resulting in bronchospasm and the other producing urticaria/angioedema. Bronchospasm is the predominant symptom of aspirin intolerance in patients who have asthma. In contrast, the predominant symptom of aspirin intolerance in patients who have rhinitis is urticaria/angioedema. In the bronchospastic type of aspirin intolerance, there is a significant correlation with an increased frequency of nasal polyposis, and with a similar age-onset of asthma and aspirin intolerance. These correlations were not present in the urticaria/angioedema type. Additional evidence for familial occurrence of aspirin intolerance is presented, and its relationship with subtypes of aspirin intolerance is discussed. In a double-blind, crossover study with normal control subjects matched by age and sex, 15% (6/40) of aspirin-intolerant individuals had significant adverse reactions to tartrazine challenge and not to the placebo. None of the 40 normal control subjects had any adverse reactions.

In our past publications,[1, 2] we presented the hypothesis that in aspirin intolerance two basic mechanisms may be present, one resulting in bronchospasm and the other producing urticaria/angioedema. We demonstrated that the predominant symptom of aspirin intolerance in patients with asthma was bronchospasm, while the predominant symptom in patients with rhinitis was urticaria/angioedema. In this investigation, we present further data to support this hypothesis. In addition, we present more evidence that aspirin intolerance may localize in certain families and offer an explanation as to one possible mechanism for this localization.

Cross-reaction between aspirin and tartrazine (FDC Yellow No. 5) was first reported in 1967[3] and confirmed several months later by Samter and Beers.[4, 5] The frequency of this cross-reactivity following tartrazine challenge in aspirin-intolerant individuals is a matter of controversy since its report in the literature has varied from 7.5% to over 87%.[4-7] As an aid in clarifying this situation, the initial purpose of this study was to determine the frequency of this cross-reactivity by challenging aspirin-intolerant patients and normal control subjects, who were matched by age and sex, with tartrazine and a placebo in a double-blind, crossover procedure using strict evaluating criteria.

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TABLE I. Major subtypes of aspirin intolerance in patients with asthma and/or rhinitis

Allergy diagnosis	Total No.	Symptoms produced by aspirin						
		No. with bronchospasm	%	P value	No. with urticaria/ angioedema	%	P value	No. with both bronchospasm and urticaria/angioedema
Asthma with or without rhinitis	28	18	64.3	<0.005	8	28.6	<0.005	2
Rhinitis (alone)	8	0	0		8	100		0
Total	36*	18	50.0		16	44.4		2

*Four patients are not included in Tables I and II because they either did not have a primary diagnosis of asthma or rhinitis (2), or aspirin ingestion resulted in severe rhinorrhea only (2).

MATERIAL AND METHODS

Our recent epidemiologic study[2] helped localize aspirin-intolerant patients through direct interviews. An attempt was made to ask all those patients in the past study to participate in the present investigation. In addition, all new cases of aspirin intolerance acquired since that study either in the Rhode Island Hospital Allergy Clinic or in private practice were also asked to participate in the present investigation. Forty patients with aspirin intolerance in the present study includes all those who volunteered for this project. Twenty patients had participated in our initial study. For a control series, 40 normal individuals with no history of asthma, rhinitis, chronic urticaria, or aspirin intolerance were matched by age and sex to the 40 patients with aspirin intolerance.

Almost all of our normal group were volunteers from our hospital staff, including clerks, aids, nurses, and physicians. With the approval of this study by our hospital committee on human research, informed consent was obtained from all individuals who agreed to participate in this study.

All individuals were challenged in a double-blind manner with two types of empty gelatin capsules, one containing 0.22 mg of tartrazine dissolved in the gelatin shell and the other containing a gelatin shell with no dyes. Both types of capsules are of the same size and shape and are a standard product of a manufacturer (Parke, Davis & Co.). After placing these individuals on a special diet that eliminated all preservatives and color additives, for about 48 hr, a nurse challenged them first with one type capsule and at least 24 hr later with the other type capsule. In these challenges, capsules were placed directly in the patient's mouth with the patient's eyes closed. Neither the subject nor the evaluating physician knew what type of capsules were taken. All subjects received a 2-capsule challenge dose of tartrazine (0.44 mg) at one time except for 2 aspirin-intolerant individuals. One of these individuals had an adverse reaction to 1 capsule of tartrazine (0.22 mg) and, therefore, the double-capsule challenge (0.44 mg) was not attempted. The other individual did not wish to continue the double-blind study with the 2-capsule challenge, but completed the 1-capsule challenge. Most of our patients were initially challenged with the 2-capsule dosage without the preliminary 1-capsule challenge.

Pulmonary function tests, total vital capacity (TVC), forced expiratroy volume in one second (FEV_1), peak flow rate (PFR), and an examination preceded each capsule challenge and were repeated 3 hr after each challenge. A positive reaction was accepted if the patient experienced objective signs of acute bronchospasm together with at least a 20% reduction in all 3 pulmonary function tests. (TVC, FEV_1, and PFR). A positive reaction was also accepted if the patient experienced generalized pruritus, urticaria, or angioedema occurring within 3 hr after the capsule challenge. Patients were also questioned about any type of delayed reaction.

Our criteria for the diagnosis of asthma, rhinitis, and aspirin intolerance were the same as in our two past studies on this subject. A diagnosis of asthma was accepted if symptoms

TABLE II. Age onset, nasal polyps, and major subtypes of aspirin intolerance in patients with asthma and/or rhinitis

Symptoms produced by aspirin	Total	No. with similar age-onset of allergy (asthma/rhinitis) and aspirin intolerance*	%	P value	No. with nasal polyps	%	P value
Bronchospasm	18	16	89	<0.005	10	55.6	< 0.01
Urticaria/ angioedema	16	4	25		2	12.5	
Both bronchospasm and urticaria/ angioedema	2	2	100		2	100	
Total	36	22	61.1		14	38.9	

*Within 1 yr of each other.

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. Cases of infectious rhinitis were excluded from this study. Vasomotor rhinitis was classified with those patients with rhinitis who had negative skin tests. Our criteria for intolerance to aspirin were acute bronchospasm, rhinorrhea, urticaria, angioedema, or shock occurring approximately within 2 hr of ingestion. Angioedema was included in the category of urticaria. A diagnosis of nasal polyposis was made by history, physical examination, or ENT consultation.

RESULTS

In the 40 patients with aspirin intolerance, there also was an additional diagnosis of asthma in 19, both asthma and rhinitis in 10, rhinitis alone in 9, and chronic urticaria in 2. Of the 38 patients with asthma and/or rhinitis, 36 had a history of reacting to aspirin by either bronchospasm or urticaria. In the remaining 2 patients, aspirin ingestion resulted in severe rhinorrhea only. The 2 patients with chronic urticaria alone as a primary diagnosis reacted to aspirin by eperiencing a dramatic exacerbation of their urticaria.

The 40 patients with aspirin intolerance consisted of 34 females and 6 males with an average age of 42.6 yr and an age range of 17 to 73 yr. The 40 normal control subjects also included 34 females and 6 males. The average age of this group was 42.2 yr with an age range of 20 to 70 yr.

Aspirin intolerance was reportedly manifested by either bronchospasm or urticaria in 28 of our patients with asthma and in 8 of the patients with rhinitis alone (Table I). Bronchospasm alone was the predominant symptom of aspirin intolerance in patients with asthma, 64.3% (18/28), while none of the patients with rhinitis alone experienced bronchospasm following aspirin ingestion ($p < 0.005$). Conversely, urticaria/angioedema was the predominant symptom of aspirin intolerance in patients with rhinitis alone, 100% (8/8), while only 28.6% (8/28) of patients with a diagnosis of asthma experienced urticaria/angioedema ($p < 0.005$).

We mainly evaluated our data by subdividing it into the 2 major types of symptoms produced by aspirin ingestion, bronchospasm and urticaria/angio-

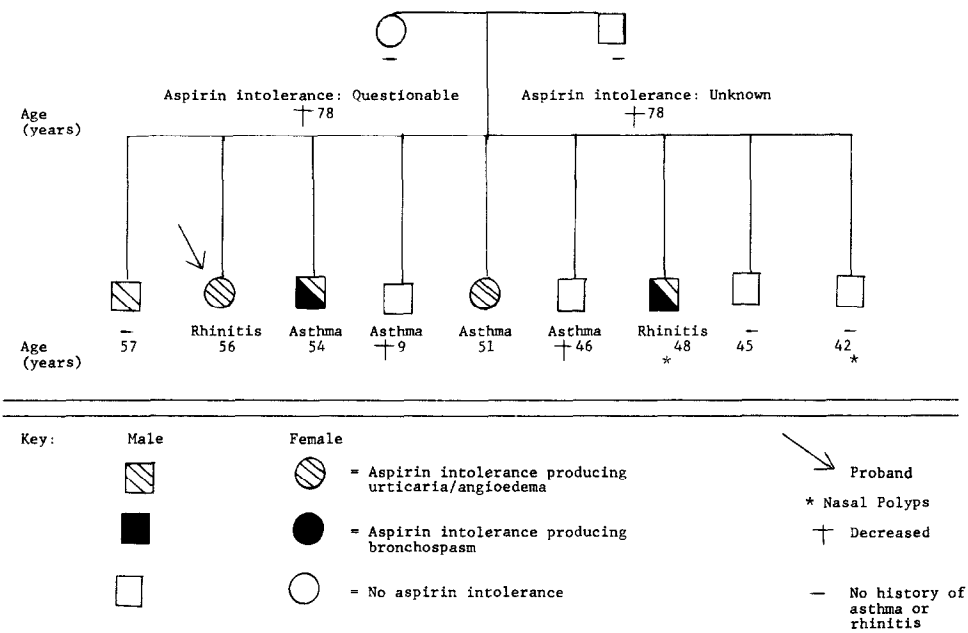

FIG. 1. Familial occurrence of aspirin intolerance (based on reliable information obtained from the proband after repeated questioning of her relatives).

edema. If aspirin ingestion produced bronchospasm, the age onset of aspirin intolerance was similar (within 1 yr) to the age onset of asthma in a majority of our cases, 89% (16/18). If the symptom produced by aspirin intolerance was urticaria/angioedema, then the age onset of aspirin intolerance was similar to the age onset of the primary diagnosis, asthma or rhinitis, in only 25% (4/16) of the patients. This difference in age onset is statistically significant ($p < 0.005$) (Table II). Further confirmation of these results revealed that the mean age onset of aspirin intolerance, 31.1 yr, in the group with bronchospasm was similar to the mean age onset of asthma, 32.1 yr, in this same group. However, the mean age onset of aspirin intolerance in the urticaria/angioedema group, 30.0 yr, was not as similar to the mean age onset of asthma or rhinitis, 34.3 yr.

Table II also demonstrates that the frequency of nasal polyps, 55.6% (10/18), is significantly greater ($p < 0.01$) in the group that responds to aspirin with bronchospasm than in the group that responds to aspirin with urticaria/angioedema, 12.5% (2/16).

There was essentially no difference in the frequency of positive allergy skin tests to a battery of inhalant allergens[1, 2] in either the bronchospastic or the urticaria/angioedema type of aspirin intolerance in patients with asthma or rhinitis.

A positive family history of aspirin intolerance was found in the immediate families of 7.5% (3/40) of our patients with aspirin intolerance. One asthmatic female whose aspirin intolerance symptom is bronchospasm has an asthmatic mother who also has acute bronchospasm following aspirin ingestion. Another asthmatic male whose aspirin intolerance symptoms is bronchospasm has an

TABLE III. Major subtypes of aspirin intolerance

	Bronchospastic type	Urticaria/angioedema type
Increased frequency in asthma	Yes	No
Increased frequency in rhinitis	No	Yes
Correlated with nasal polyposis	Yes	No
Similar age onset as asthma	Yes	No
Increased frequency in older age groups	Yes	No
Familial occurrence	Yes	Yes

asthmatic sister who developed urticaria/angioedema following aspirin ingestion. The third patient is a female who has rhinitis and has urticaria/angioedema as a result of aspirin ingestion. In her family, 5 out of 9 siblings have aspirin intolerance (Fig. 1). Three siblings have the urticaria/angioedema type of aspirin intolerance and 2 siblings have both the bronchospastic and the urticaria/angioedema type of aspirin intolerance. In addition, the mother of this family reportedly stated that aspirin made her "sick"; however, the type of symptoms produced by aspirin is unknown. Also one of the normal male siblings, 45 years of age, has an asthmatic son, 22, with the urticaria/angioedema type of aspirin intolerance. None of the 40 normal, matched, individuals in this study have a family history of aspirin intolerance.

Of our aspirin-intolerant individuals, 15% (6/40) reacted adversely to the tartrazine challenge and not to the placebo. None of the 40 normal control subjects reacted adversely either to the tartrazine challenge or to the placebo. The adverse reaction to tartrazine was similar to the type of reaction aspirin produced in these patients. In 3 out of 6 patients in whom tartrazine produced symptoms of generalized itch or urticaria, aspirin also produced urticaria. In the remaining 3 patients, tartrazine produced acute bronchospasm; in these patients aspirin also produced bronchospasm, except in one case in which aspirin produced both bronchospasm and urticaria. Cross-reactions between tartrazine and aspirin intolerance occurred essentially equally in each of the two major subtypes of aspirin intolerance.

The adverse reactions to tartrazine responded well to immediate treatment. The bronchospasm reactions were moderate and the urticaria reactions were mild to moderate. There was one questionable mild delayed reaction to the tartrazine challenge, and this was classified as a negative reaction. All of these adverse reactions occurred with the double-dose capsule (0.44 mg) of tartrazine except in 1 patient, whose primary diagnosis was chronic urticaria with no history of asthma or rhinitis. She reacted to 1 capsule of tartrazine (0.22 mg).

DISCUSSION

We reported previously that the frequency of aspirin intolerance is significantly greater in asthmatic patients (3.8%) than in rhinitis or normal individuals (0.9%).[2] Similar to our past reports,[1, 2] our present data also demonstrate that in aspirin intolerance the symptom of bronchospasm is found predominantly in patients with asthma while the symptom of urticaria/angioedema is found predominantly in patients with rhinitis. Our past reports

also demonstrated that the progressive increase of aspirin intolerance with advancing years was directly related to the bronchospastic type of symptomatology and not to the urticaria/angioedema type of symptoms.

For these reasons, we felt that there probably are at least two different mechanisms of aspirin intolerance, one producing bronchospasm, the other producing urticaria/angioedema. This hypothesis is supported by the additional evidence in the present study that the bronchospastic type of aspirin intolerance has a similar age onset as the asthma, and has a significantly greater frequency of nasal polyposis than does the urticaria/angioedema type of aspirin intolerance. It seems, therefore, that in the bronchospastic type of aspirin reaction, the development of aspirin intolerance may be related to the same disease process as the developement of asthma. It is still speculative as to whether this disease process involves the kinins, prostaglandins, or other systems. It appears, however, that the asthmatic with a bronchospastic type of aspirin intolerance may represent a peculiar or different kind of asthma, with a high frequency of nasal polyposis, increased frequency in older age groups, and similar age onset of aspirin intolerance (Table III). This type of asthma should probably be classified as aspirin-asthma and should not include the urticaria/angioedema type of aspirin intolerance.

Occasional clustering of aspirin intolerance in a few families has been noted in the literature.[8, 9] A review of these cases reveals that the bronchospastic type of aspirin intolerance was present and usually only 2 members of an immediate family were affected. However, in one family our finding that 5 out of 9 children have aspirin intolerance appears to be unusually high (Fig. 1). Both the bronchospastic and urticaria/angioedema types of aspirin intolerance are present in this family. It is possible that the bronchospastic and urticaria/angioedema types of aspirin intolerance are transmitted by 2 separate genes and the chance occurrence of both genes in the same gene pool of one family may account for the exceptionally high number of siblings afflicted with aspirin intolerance. It is noteworthy that in our normal control group, there was no family history of aspirin intolerance. Whether separate genetic mechanisms may account for the different symptoms of aspirin intolerance, or whether a single genetic mechanism is the basis for the varied symptomatologic manifestations remains for speculation. It may be profitable to investigate the genetic aspects of aspirin intolerance in greater detail in future work.

Tartrazine (FDC Yellow No. 5) is a color additive that has a widespread use in foods and medications. It has been estimated that the maximum ingested dose per capita is 16.3 mg per day.[10] The first reported adverse reaction to color additives was in 1958 when Speer[11] reported that color additives caused asthma in 6 children. In 1959, Lockey[12] reported that tartrazine caused hives in 3 patients. Recently, interest was renewed in the frequency of cross-reactivity of tartrazine in aspirin-intolerant individuals.[6, 7] We are unable to confirm the exceptionally high frequency of cross-reactivity reported in these recent studies. However, this difference may be due to the altered dietary habits found in different countries. Our results of 15% cross-reactivity resembles the only other explicitly stated double-blind, large study in the literature, Samter and Beers,[4]

who reported 7.5%. However, these authors presented their data only in summary form. Most of the studies on this subject were not done in a double-blind manner.

The fact that the type of symptom produced by tartrazine was similar to that produced by aspirin may mean that the same type of biochemical abnormality may be present. This similarity of symptoms may also serve as confirmation of the partial cross-reactivity between these 2 chemicals. However, the molecular structure of tartrazine is vastly different than that of aspirin, and the exact mechanism of this cross-reactivity still remains largely unknown.

Our challenge dose of tartrazine was relatively low (0.22 mg to 0.44 mg). Other authors have used 1 to 5 mg, and Samter and Beer reportedly used 25 mg. However, a dose as low as 0.15 mg of tartrazine, as found in Premarin, 1.25 mg, has been known to cause adverse reactions to tartrazine.[3] Samter and Beers, who used a 50 times[4] larger dose than in our study, did not find a greater frequency of cross-reactivity. We emphasize that future studies evaluating adverse reactions of tartrazine and other food additives should employ a strict double-blind procedure and rigorous objective criteria.

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