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Non-steroidal anti-inflammatory drug hypersensitivity in adults and the factors associated with asthma

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KEYWORDS
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Summary
Background: Characteristics of non-steroidal anti-inflammatory drug (NSAID)-hypersensitivity (NH) associated with underlying/accompanying diseases has not been studied in Turkey. In addition, the factors associated with asthma in NH patients are not well known. The present study aimed to investigate the relationship between NH and chronic urticaria, rhinitis/rhinosinusitis, and asthma in an effort to identify NH phenotypes. The study's secondary aim was to identify the factors associated with asthma in NH patients and the NSAID reaction pattern in asthmatics.
Methods: Data for 1137 NH patients in our hospital's allergy clinic database were retrospectively analyzed. Patients were divided into 5 groups based on their accompanying diseases (chronic urticaria, asthma, rhinitis/rhinosinusitis). Asthmatic patients were compared to non-asthmatic patients to identify the factors associated with asthma.
Results: Reaction patterns and patient characteristics in each group differed from those in the reference group (NH only group). Asthma in patients with NH was associated with female gender, sinonasal polyposis/polyp surgery, rhinitis/rhinosinusitis, NSAID-induced rhinitis/asthma or a blended reaction pattern, immediate reaction following NSAID intake, self-reported history of food allergy, and family history of asthma; the odds ratios and 95% CIs were 1.35 (1.02–1.78), 13.52 (8.74–20.9)/10.94 (6.73–17.77), 12.06 (9–16.17), 15.28 (10.45–22.36)/2.43 (1.70–3.45), 1.76 (1.31–2.35), 1.49 (1.04–2.14), and 3.1 (2.35–4.08), respectively. The characteristics of the asthmatic patients that had urticaria/angioedema-type reactions to NSAID intake (pseudo Samter's syndrome) differed from those in the asthmatics with rhinitis/asthma-type reactions.

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Conclusions: Chronic urticaria, rhinitis, and asthma commonly accompany NH. NSAID response patterns in NH patients may help differentiate groups of patients. The present study identified factors associated with asthma in NH patients and observed that there seems to be different phenotypes of Samter's syndrome, for which a new classification scheme was proposed.
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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) account for 21%—25% of adverse drug events, and are the second most common cause of drug-induced hypersensitivity reactions.[1,2] A recent EAACI/ENDA group review published data on the pathomechanisms and clinical spectrum of hypersensitivity reactions caused by NSAIDs.[1] Depending on the diagnostic methods used and study design, NSAID-hypersensitivity (NH) in adult asthmatic patients, patients with bronchial asthma and nasal polyps, and patients with chronic urticaria can be as high as 21%, 25.6%, and 35%, respectively; however, despite these high prevalences there is lack of knowledge of the predictors of the clinical course of NH, which could be of critical importance to clinicians.[3—5]

Aspirin, one of the most commonly consumed NSAIDs, can induce wheals/angioedema in patients with chronic urticaria via inhibition of COX-1.[6] Such eicosanoid alterations in patients with chronic idiopathic urticaria and aspirin sensitivity are similar to those observed in aspirin-exacerbated respiratory disease (AERD).[7] Although the pathomechanisms of aspirin-induced urticaria/angioedema and AERD appear similar, there should be some differences, or the 2 are different phenotypes of the same disease.

The presence of asthma and aspirin-induced asthmatic symptom exacerbation is commonly referred as Samter's syndrome, aspirin-induced asthma, or AERD.[8,9] There is also a sub-group of patients with asthma and NH that experience urticaria/angioedema-type reactions instead of bronchospasm in response to NSAIDs. The proportion of this sub-group among asthmatics with NH is unknown; these patients may constitute a different spectrum of Samter's syndrome.

Characterizing NH can help improve clinician's ability to determine a prognosis and disease course. Some patients can go into remission when the underlying disease subsides, whereas asthma and/or rhinitis and/or chronic urticaria can occur during the course of NH. As such, the present study aimed to investigate the relation between NH and chronic urticaria, rhinitis/rhinosinusitis, and asthma, and to define NH phenotypes. The study's secondary aim was to identify the factors associated with asthma in NH patients and the NSAID reaction pattern of asthmatics.

Materials and methods

Data collection

Data for 1137 patients diagnosed with NH-with or without concurrent asthma, rhinitis/rhinosinusitis, and chronic urticaria-that presented to Hacettepe University, School of Medicine, Adult Allergy Clinic, Ankara, Turkey, between January 1991 and December 2010 were retrospectively reviewed using the allergy clinic database. Data in the database were collected prospectively. Patient age, gender, NSAID reaction patterns, accompanying diseases (rhinitis/rhinosinusitis, asthma, chronic urticaria, and metal allergy), family history of asthma/rhinitis/rhinosinusitis/NH, self-reported NSAID reaction patterns, age of onset of NH/asthma/rhinitis, and diagnostic work-up findings were recorded in the allergy clinic database. Asthma and rhinitis were diagnosed by allergy specialists at the study center based on international and national asthma/rhinitis guidelines (GINA, ARIA and national guidelines), and the diagnosis and surgical treatment of nasal polyps was made by otorhinolaryngologists at the same center. Chronic urticaria was defined as spontaneous wheals and/or angioedema >6weeks in duration.[10]

Patients

A reliable clinical history of ≥2 events with the same NSAID or ≥2 events with unrelated NSAIDs, or in case of an unreliable history, a positive oral challenge with the tested NSAID were required for the diagnosis of NH. Patients with delayed-type (reaction after 24 h of NSAID intake) skin or systemic reactions to NSAIDs were not recorded into the database. Single-blind oral drug provocation tests were performed to confirm the diagnosis of NH (in cases with an unreliable history) and/or to identify alternative analgesics (in cases of a reliable history) following presentation to the allergy clinic.[1] As this is a data review study, all patients diagnosed as NH between January 1991 and December 2010 were included in the analysis. All patients met the indication criteria for drug provocation testing described by the European Network for Drug Allergy and European Network on Hypersensitivity to Aspirin and Non-steroidal Anti-Inflammatory Drugs.[1,11] Written informed consent was obtained from each patient before each provocation test and the study protocol was approved by the Hacettepe University Ethics Committee (HEK 12/188-38).

While identifying safe alternative analgesics for patients that did not reside in Ankara, in order to minimize cost and manpower expenditures some patients were tested via the **Hacettepe method** (triple test) starting in September 2002.[12,13] Patients that were tolerant to a limited number of alternative analgesics (e.g. only paracetamol) were tested with codeine.[14]

Patients were divided into the following 5 groups: NH-N: NH with no underlying disease (reference group); NH-A: NH with asthma; NH-U: NH with chronic urticaria; NH-R: NH with rhinitis; NH-O: NH and any combination of rhinitis, asthma, and chronic urticaria.

Based on each patient's history, NSAID reaction patterns were classified as follows: anaphylaxis, urticaria/angioedema, rhinitis/asthma, and blended reactions

(any combination of the listed patterns other than anaphylaxis).[15,16] Asthmatic patients were compared to non-asthmatic patients in order to identify factors associated with asthma.

Pseudo Samter's syndrome was considered NSAID-induced urticaria/angioedema in an asthmatic patient, and Samter's syndrome was considered NSAID-induced anaphylaxis, rhinitis/asthma, or blended reactions in an asthmatic patient.

Statistics

Statistical analysis was performed using SPSS v.18.0 for Windows. Categorical variables were expressed as a frequency, versus mean ± SD for continuous variables. Chi-square analysis was used to test differences between nominal variables and the *t*-test was used for interval variables between two groups. The level of statistical significance was set at $p < 0.05$. Variables were analyzed using logistic regression with adjustment for age and gender to identify independent associations with asthma.

Results

Patients

The study included 1137 patients with data entered in the database. In all, 416 (36.6%) of the patients were in the NH-N group (reference group), 64 (5.6%) were in the NH-A group, 142 (12.5%) were in the NH-U group, 134 (11.8%) were in the NH-R group, and 381 (33.5%) were in the NH-O group (Table 1). Mean age of the study population (72.6% female and 27.4% male) was 39.99 ± 12.4 years (range: 16–86 years). Mean age of onset of rhinitis, asthma, and NH were 28.1 ± 11.9 years, 32.4 ± 12.4 years, and 34.2 ± 12.8 years, respectively. Rhinitis/rhinosinusitis/nasal polyposis were common among the asthma patients (68%) (Fig. 1).

Groups characteristics and comparison with the reference group (NH-N)

The most common reaction pattern to NSAIDs was urticaria/angioedema (56%). The predominant reaction pattern was urticaria/angioedema in the NH-N and NH-U groups (75% and 83%, respectively), versus NSAID-induced rhinitis/asthma in the NH-O group (45%). Based on patient histories, reactions to NSAIDs occurred <1 h after intake in 72% of the patients. The characteristics of the NH-O group differed from those in the NH-N (reference) group (Table 1).

Drug provocation tests

In order to prove NH and/or to identify alternative analgesics 545 oral challenges were performed with meloxicam, 431 with paracetamol, 409 with nimesulide, 321 with

Table 1 Characteristics of the patient groups and comparison with the reference group (NH-N group[a]).

Total *n* (%)	NH-N[a] 416 (37)	NH-A[a] 64 (6)	P^1	NH-U[a] 142 (12)	P^2	NH-R[a] 134 (12)	P^3	NH-O[a] 381 (33)	P^4
Age at registration in database, mean ± SD	39.6 ± 13	43 ± 14	0.05	40 ± 12	0.62	38 ± 11	0.2	40.5 ± 12	0.3
Female/male %	70/30	80/20	0.12	71/29	0.79	72/28	0.6	75/25	0.1
Self-reported reaction type[b] *n* (%)									
• Anaphylaxis: 128 (11)	53 (13)	7 (11)	0.69	16 (11)	0.65	17 (13)	0.1	35 (9)	0.11
• Rhinitis/asthma: 229 (20)	9 (2)	23 (36)	**<0.001**	2 (2)	0.58	25 (19)	**<0.001**	170 (45)	**<0.001**
• Urticaria/angioedema: 631(56)	312 (75)	26 (41)	**<0.001**	118 (83)	**0.04**	73 (55)	**<0.001**	102 (27)	**<0.001**
• Blended: 148 (13)	42 (10)	8 (12)	0.56	6 (4)	**0.03**	18 (13)	0.27	74 (19)	**<0.001**
Time to onset of reaction *n* (%)									
• <1 h: 789 (72)	265 (66)	46 (74)	0.21	90 (66)	1	99 (77)	**0.02**	289 (79)	**<0.001**
• 1–6 h: 276 (25)	116 (29)	16 (26)	0.6	43 (32)	0.56	26 (20)	0.05	75 (20)	**0.006**
• 6–24 h: 28 (3)	19 (5)	0	NA	3 (2.2)	0.2	3 (2)	0.24	3 (1)	**0.001**
Antibiotic hypersensitivity: 198 (17.4)	93 (22)	11 (17)	0.35	21 (15)	0.05	16 (12)	**0.009**	57 (15)	**0.008**
Food allergy: 141 (12.4)	38 (9)	10 (16)	0.11	22 (15)	**0.03**	12 (9)	0.9	59 (15)	**0.006**
Metal allergy: 166 (14.6)	41 (10)	10 (16)	0.16	41 (29)	**<0.001**	13 (10)	0.96	61 (16)	**0.009**

Comparisons were made via the chi-square test for categorical variables and the *t* test for continuous variables, where appropriate.
P^1: Comparison between the NH-A and NH-N groups.
p^2: Comparison between the NH-U and NH-N groups.
p^3: Comparison between the NH-R and NH-N groups; p^4: Comparison between the NH-O and NH-N groups.
NA: Not applicable.
The *p* values <0.05 are indicated in bold.
[a] NH–N: NH with no underlying disease (reference group); NH-A: NH with asthma; NH-U: NH with chronic urticaria; NH-R: NH with rhinitis; NH–O: NH and any combination of rhinitis, asthma, and chronic urticaria.
[b] A patient that did not report a reaction pattern.

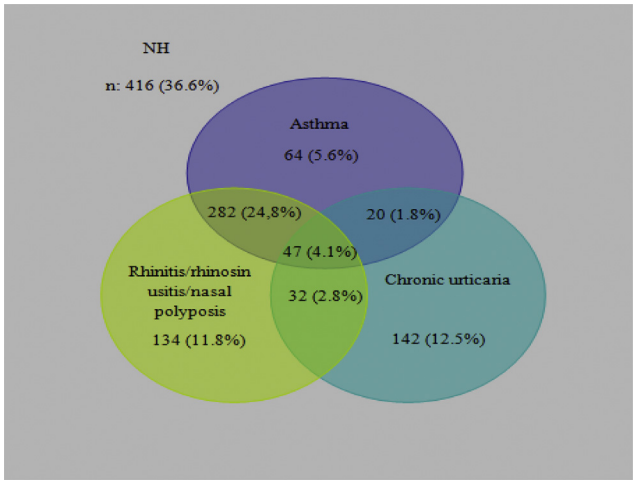

Figure 1 Accompanying/underlying diseases in the NH patients.

codeine, 173 with benzydamine, 162 with aspirin, 159 with rofecoxib, and 26 with nabumetone.

Among the 278 patients that reported having adverse reactions to paracetamol, 91 were challenged with paracetamol due to an unreliable history, and only 26 tested positive (28.6%); however, 568 patients reported having adverse reactions to aspirin, 61 were challenged with aspirin due to an unreliable history, and 90% tested positive (Table 2). The number of challenges shown in Table 2 may seem low, but those drugs are COX-1 inhibitors and a history of 2 episodes with the same drug or 2 episodes with 2 different drugs is sufficient for a diagnosis of NH.

Two patients had severe respiratory reactions after aspirin provocation and were admitted to the intensive care unit for follow-up; both were discharged the following day. None of the patients in the study had local or general anesthesia-related allergy as we reported before.[17]

Factors associated with asthma

The 724 patients without asthma were compared to the 413 patients with asthma. Table 3 shows the factors that were associated with asthma in the NH patients. Female gender, accompanying rhinitis/rhinosinusitis, nasal polyposis, history of polyp surgery, NSAID-induced rhinitis/asthma or blended reaction, immediate reaction (<1 h after intake), food allergy, and family history of asthma were associated with asthma. History of smoking, the presence of chronic urticaria, NSAID-induced urticaria/angioedema or anaphylaxis, NSAID reactions 1–6 h after intake, antibiotic allergy, and family history of drug and NSAID allergy were associated with the non-asthmatic NH phenotype.

Among the 413 NH patients with asthma, 109 (26.4%) had NSAID-induced urticaria/angioedema-type reactions and were categorized as pseudo Samter's syndrome, and 304 (73.6%) had NSAID-induced anaphylaxis, rhinitis/asthma, or blended reactions, and were categorized as Samter's syndrome. Table 4 shows a comparison between these 2 subgroups. Interestingly, more patients with pseudo Samter's syndrome had a positive skin prick test, metal allergy, antibiotic allergy, and chronic urticaria, were female, and presented at a younger age.

Discussion

In the present study NH patients were grouped based on accompanying chronic urticaria, asthma, and rhinitis/rhinosinusitis, and differences between the groups were identified. This study also analyzed the factors associated with asthma in NH patients and a new classification scheme for Samter's syndrome was proposed. It is known that a particular NSAID can induce different types of reactions in different organ systems in the same and in different individuals.[16] Some patients may develop a respiratory reaction to an NSAID first, and then develop asthma and/or rhinitis, as well as chronic urticaria. An asthmatic NH patient can exclusively experience urticaria/angioedema in reaction to NSAIDs, as was observed in the present study; among 413 NH patients with asthma, 109 (26%) had exclusively urticaria/angioedema-type reactions to NSAIDs (pseudo Samter's syndrome). The clinical course and prognosis in such patients is unknown, and it remains unclear if they go into remission or develop rhinitis/asthma-type reactions later during the course of NH. In the present study, patients with pseudo Samter's syndrome more frequently have accompanying chronic urticaria compared to patients with Samter's syndrome (30.3% versus 11.2%). It was reported that when aspirin-tolerant asthmatics were compared to those that were aspirin-intolerant (experiencing cough or dyspnea after taking NSAIDs), the rate of aspirin-induced urticaria, atopic dermatitis, and rhinosinusitis was higher in the aspirin-intolerant group.[18]

Celik et al. studied 190 NH patients in Turkey and reported that asthmatic and urticarial reactions were more common in the patients with asthma and chronic urticaria, respectively.[19] In the present study the prevalences of chronic urticaria, asthma, and rhinitis were high; when

Table 2 Self-reported NSAID and paracetamol adverse reactions and oral provocation test results.

	Reported as safe			Self-reported adverse reaction		
NSAIDs	Total *n*	Challenged *n*	Positive challenge *n* (%)	Total *n*	Challenged *n*	Positive challenge *n* (%)
ASA	75	10	1 (10)	568	61	55 (90)
Paracetamol	401	62	0	278	91	26 (28.6)
Metamizol	57	0	–	480	7	5 (71.4)
Naproxen	56	1	0	302	6	5 (83.3)
Flurbiprofen	7	0	–	89	5	4 (80)

Table 3 Comparison of asthmatic and non-asthmatic NH patients to identify factors associated with asthma.

n (%)	Total 1137 (100)	Asthmatic 413 (100)	Non-asthmatic 724 (100)	*p*[a]	Or (95% CI)[a]
Female %	72.6	76.3	70.6	**0.035**	**1.35 (1.02-1.78)**
History of smoking	362 (31.8)	107 (25.9)	255 (35.2)	**0.006**	**0.67 (0.51–0.89)**
Chronic urticaria	241 (21.2)	67 (16.2)	174 (24)	**0.002**	**0.60 (0.44–0.83)**
Rhinitis/rhinosinusitis	475 (41.8)	316 (76.5)	159 (22)	**<0.001**	**12.06 (9–16.17)**
Nasal polyposis	168 (14.8)	140 (33.9)	28 (3.9)	**<0.001**	**13.52 (8.74–20.9)**
Polyp surgery	124 (10.9)	102 (24.7)	22 (3)	**<0.001**	**10.94 (6.73–17.77)**
NSAID-induced urticaria/angioedema	631 (55.5)	108 (26.2)	523 (72.3)	**<0.001**	**0.13 (0.10–0.17)**
NSAID-induced rhinitis/asthma	229 (20.2)	191 (46.2)	38 (5.3)	**<0.001**	**15.28 (10.45–22.36)**
NSAID-induced blended reaction	148 (13)	80 (19.4)	68 (9.4)	**<0.001**	**2.43 (1.70–3.45)**
NSAID-induced anaphylaxis	128 (11.3)	34 (8.2)	94 (13)	**0.014**	**0.59 (0.39–0.9)**
Immediate reaction to NSAIDs (<1 h)	789 (72.2)	314 (78.9)	475 (68.3)	**<0.001**	**1.76 (1.31–2.35)**
Reaction in 1–6 h	276 (25.3)	82 (20.6)	194 (27.9)	**0.007**	**0.67 (0.50–0.89)**
Metal allergy	166 (14.6)	60 (14.5)	106 (14.6)	0.818	0.96 (0.67–1.36)
Antibiotic allergy	198 (17.4)	59 (14.3)	139 (19.2)	**0.018**	**0.67 (0.48–0.93)**
Food allergy	141 (12.4)	64 (15.5)	77 (10.6)	**0.028**	**1.49 (1.04–2.14)**
Family history of drug allergy	66 (5.8)	9 (2.2)	57 (7.9)	**<0.001**	**0.25 (0.12–0.52)**
Family history of NH	90 (7.9)	22 (5.3)	68 (9.4)	**0.010**	**0.52 (0.31–0.85)**
Family history of chronic urticaria	47 (4.1)	12 (2.9)	35 (4.8)	0.153	0.61 (0.31–1.2)
Family history of asthma	291 (25.6)	164 (39.7)	127 (17.5)	**<0.001**	**3.1 (2.35–4.08)**
Skin prick test[b]	211 (30)	93 (31.1)	118 (29.2)	0.437	1.14 (0.82–1.59)

The *p* values <0.05 are indicated in bold.
[a] *p* values and ORs were adjusted for age and gender for logistic regression analysis.
[b] Skin prick test was performed in 299 NH patients with asthma and in 404 NH patients without asthma.

Table 4 Comparison of the characteristics in the patients with Samter's and pseudo Samter's syndrome.

	Pseudo Samter's syndrome *n* = 109	Samter's syndrome/ AERD *n* = 304	*p*
Male/female %	15.6/84.4	26.6/73.4	**0.020**
Presence of rhinitis/rhinosinusitis	68 (62.4)	248 (81.6)	**<0.001**
Presence of nasal polyps	10 (9.2)	130 (42.8)	**<0.001**
Presence of chronic urticaria	33 (30.3)	34 (11.2)	**<0.001**
Disease order[a] *n* (%)			
-First asthma then NH	55 (66.3)	184 (78.3)	**0.029**
Age at registration in database (years)	39.1 ± 12	41.9 ± 12	**0.041**
Age at onset of symptoms of rhinitis (years)	28.6 ± 10.3	29 ± 12.2	0.804
Age at onset of symptoms of asthma (years)	31.8 ± 12.2	32.6 ± 12.5	0.562
Age at nasal polyps diagnosis (years)	32.7 ± 9.6	33.6 ± 11.4	0.817
Age at onset of NH symptoms (years)	33.6 ± 12	36.1 ± 12.6	0.075
Oral steroid-dependent asthma[b]	3 (4.8)	12 (6.2)	0.694
Immediate reaction to NSAIDs (<1 h)[c]	71 (67.6)	243 (82.9)	**0.001**
Antibiotic allergy	28 (25.7)	31 (10.2)	**<0.001**
Metal allergy	26 (23.9)	34 (11.2)	**0.001**
Food allergy	22 (20.2)	42 (13.8)	0.115
Family history of rhinitis	13 (11.9)	31 (10.2)	0.616
Family history of asthma	45 (41.3)	119 (39.1)	0.695
Family history of NH	8 (7.3)	14 (4.6)	0.27
Positive skin prick test[d]	29 (40.8)	64 (28.1)	**0.042**
History of polypectomy/endoscopic sinus surgery	8 (7.3)	94 (30.9)	**<0.001**

The *p* values <0.05 are indicated in bold.
[a] Patients in which asthma and NH developed simultaneously were not included (*n* = 95).
[b] Steroid dependence was based on patient files, and data are available for 256 (62%) patients.
[c] Time to reaction after NSAID intake was recorded in 398 patients and the percentages are given based on recorded cases.
[d] Skin prick testing was performed in 71 (65%) of the patients with pseudo Samter's syndrome and in 228 (75%) of the patients with Samter's syndrome.

compared to patients without an underlying disease (the NH-N group) the most common (but not exclusive) reaction pattern in the asthmatic patients was rhinitis/asthma, and food and metal allergies were more common in the patients with underlying chronic urticaria. Patients with ≥2 underlying diseases (the NH-O group) were different in most respects. It is possible that NH patients can move from one characteristic reaction group to another, and can even achieve remission.[6,20,21] Underlying/accompanying chronic urticaria/asthma/rhinitis defines the reaction pattern to NSAIDs, and NH can even become less severe when underlying/accompanying diseases go into remission.

The diagnosis of NH is based on a reported history of adverse reactions to aspirin and/or other NSAIDs.[1] Provocation testing is required to confirm or exclude hypersensitivity in cases with an unreliable history.[15,22] A finding of note in the present study is that 91 oral challenges with paracetamol were performed in patients with an unreliable history history and only 28.6% were positive. Paracetamol is present as an ingredient in many NSAID medications, which may have contributed to the high rate of false-reported adverse reactions to paracetamol in the present study. Additionally, because of anxiety, a group of patients may have reported that paracetamol was nonsafe. Currently, we are conducting a prospective study to evaluate the level of anxiety in patients with drug hypersensitivity reactions.

Some patients initially have a rhinitis/asthma-type reaction to NSAIDs, and then develop asthma during the following years.[22] Risk factors for the development of asthma are not well known. We previously reported that nasal polyposis, rhinosinusitis, and NH in childhood are associated with the subsequent development of asthma in patients with NH, and when compared to asthmatic patients analgesic-intolerant asthmatic patients more commonly had dermographism, chronic urticaria, antibiotic, metal, and food allergies, high serum total IgE level, and higher cumulative analgesic consumption.[23–25] In addition to nasal polyposis and rhinitis/rhinosinusitis in the present study population, we observed that female gender, history of polyp surgery, NSAID-induced rhinitis/asthma or a blended reaction pattern, reaction <1 h after NSAID intake, history of food allergy, and family history of asthma were the factors associated with asthma. A recently published study from Korea reported that 5.8% of asthma patients have NH, and when compared to aspirin-tolerant patients they observed that the aspirin-induced urticaria rate was significantly higher in the patients that were aspirin intolerant (49.2% and 2.7%, respectively $p < 0.001$).[18]

There are many published classification schemes for NH reactions.[1,2,15,16,26,27] As such, we propose a classification based on clinical characteristics and reaction patterns observed in the present study's Turkish patients.

Asthmatic attacks and/or nasal symptoms caused by NSAIDs is defined as AERD, which is also referred to as aspirin triad, asthma triad, Widal syndrome, Samter's syndrome, aspirin-induced asthma, aspirin-intolerant asthma, and aspirin-sensitive rhinosinusitis/asthma syndrome.[1,9] We previously reported that AERD patients are heterogeneous and must be classified, and a classification scheme (Kalyoncu classification) proposed.[27,28] In the present study, we proposed a new classification scheme for Samter's syndrome (Fig. 2). To the best of our knowledge this is the first use of the term pseudo Samter's syndrome; however, 26.4% of the present study's NH patients with asthma had NSAID-induced urticaria/angioedema and were classified as pseudo Samter's syndrome, NH patients with asthma and NSAID-induced rhinitis/asthma-type reactions were classified as Samter's syndrome, as the sine qua non for the

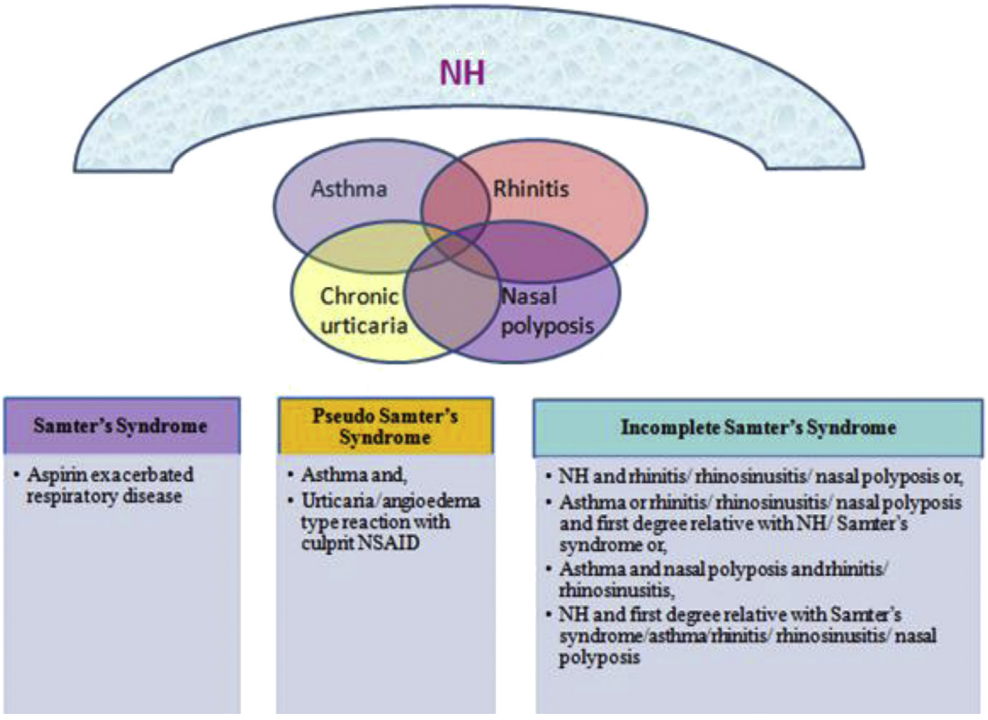

Figure 2 Classification scheme for Samter's syndrome (Kalyoncu classification).

diagnosis of Samter's syndrome is the presence of asthma and COX enzyme-mediated aspirin-induced exacerbation of asthma. In addition, there might be incomplete forms of the disease; in such cases rhinitis/rhinosinusitis/nasal polyposis can accompany NH without asthma. Although clinicians are aware of the incomplete forms of Samter's syndrome, the clinical course is not well known. Incomplete forms of Samter's syndrome were classified separately in the present study. Prospective cohort studies are required to further evaluate incomplete Samter's phenotypes.

Although the guideline-based and patient reported asthma control level was similar between Europe and Turkey, the oral steroid-dependent asthma rate in the present study's patients with Samter's syndrome was much lower than reported earlier.[9,29,30] One comparable study published in 2000, reported that the steroid-dependent asthma rate in patients with AERD was 51.4%, and that 80% of the study population used inhaler corticosteroids for chronic asthma.[9] All the patients with Samter's syndrome in the present study were using inhaler steroids. Although, it is not known why the oral steroid-dependent asthma rate in the present study was so much lower, genotype differences could be a reason.

The level of biomarkers that could have classified the present study's patients more accurately was not studied, which is a limitation of the study. Previous classification studies did not examine biomarkers, and classification studies have primarily been based on clinical characteristics.[1,9,15,16] The comparison of the severity of asthma between groups, and the natural course of the phenotypes could not be analyzed because of the retrospective nature of the study.

In conclusion, chronic urticaria, rhinitis, and asthma were common among the present study's NH patients; in some cases they preceded NH and in others they developed during the course of NH, the natural course of which remains to be fully known. NSAID response patterns in NH patients may help differentiate groups of patients. The present study identified factors associated with asthma in NH patients and observed that there seems to be different phenotypes of Samter's syndrome, for which a new classification scheme was proposed. Additional research is required to more clearly delineate the behavior and natural course of pseudo Samter's syndrome, as well as incomplete forms of the disease.

Conflict of interest

All authors declare no conflict of interest relevant to this study. No financial support for the research was received. The study was presented as an abstract in XIX. National Allergy and Clinical Immunology Congress (07—11 November 2012, Antalya/Turkey).

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