

Association between Asthma, Rhinitis and NSAID Hypersensitivity in Chronic Urticaria Patients and Prevalence Rates

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Key Words

Asthma • Chronic urticaria • Drug allergy • Nasal polyps • NSAID hypersensitivity • Rhinitis • Urticaria

Abstract

Background: The coexistence of allergic diseases and chronic urticaria (CU) is not uncommon. Our aim was to show the prevalence of allergic diseases in chronic urticaria patients and whether possible risk factors precipitate the development of these conditions. **Methods:** The data of 953 patients diagnosed with CU in our adult allergy clinic between January 1991 and June 2006 were retrospectively evaluated. **Results:** The mean ages of the CU patients with and without non-steroidal anti-inflammatory drug hypersensitivity (NSAIDH) were 39.0 ± 11.8 and 36.7 ± 12.3 , respectively ($p = 0.014$). There was a female predominance in both groups (74.6 and 68.2%, respectively, $p = 0.06$). Apparently, some conditions occurred significantly more often in CU patients with NSAIDH compared to those without NSAIDH: 16.4 and 8.4% for asthma ($p < 0.001$), 4.2 and 0.8% for nasal polyps ($p < 0.01$), 20.8 and 7.3% for antibiotic hypersensitivity ($p < 0.001$), 21.6 and 12.3% for metal sensitization ($p < 0.01$), and 8 and 0.6% for familial NSAIDH ($p < 0.001$), respectively. Dermographism was more common in CU patients without

NSAIDH compared to those with NSAIDH (29.4 and 21.2%, respectively; $p < 0.05$). NSAIDH increased the risk of asthma and rhinitis development [odds ratios: 52.9 (18.1–154.6) and 5.2 (2.0–13.4)]. **Conclusion:** Based on our data, the incidence rates of asthma, nasal polyps, antibiotic hypersensitivity, metal sensitization and familial NSAIDH are increased in patients with CU with NSAIDH compared to those with CU only. Coexistence of NSAIDH and CU increases the risk of developing asthma and rhinitis.

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Introduction

Urticaria, which affects nearly 15–25% of the general population, is characterized by the rapid appearance of wheals and/or angioedema and classified as chronic urticaria (CU) if activity continues for >6 weeks [1, 2]. Although several conditions such as hypersensitivity to foods, additives and drugs, and infections or internal diseases may be associated with urticarial symptoms, the cause of CU remains unknown in almost 70–80% of cases [3, 4].

The prevalence of non-steroidal anti-inflammatory drug (NSAID) hypersensitivity (NSAIDH), which is <1%

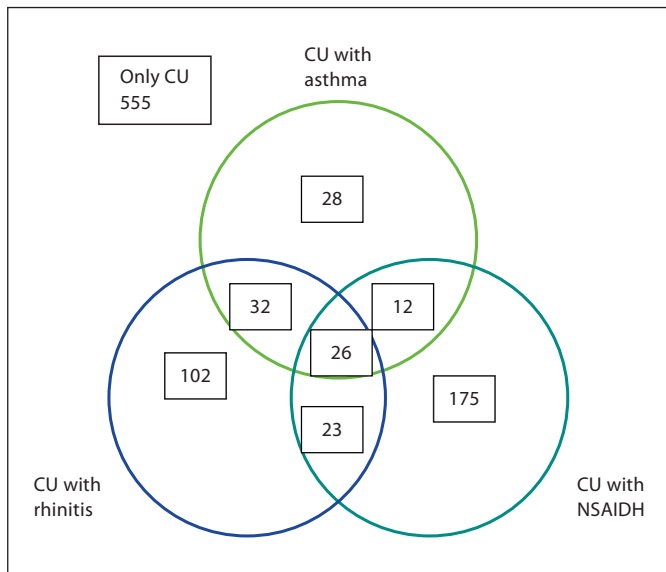


Fig. 1. The Venn diagram of CU patients according to the coexistence of other diseases.

in the general population, is much more common in certain risk groups, e.g. patients with bronchial asthma, CU and nasal polyps [5–10]. Aspirin or NSAIDs may cause acute episodes of urticaria, act as a cofactor to urticarial reactions to food or exercise, or aggravate preexisting urticaria in one third of the patients with urticaria [11].

Coexistence of allergic diseases and CU is not uncommon. Our aim was to determine the frequency of allergic diseases accompanying CU and whether possible risk factors precipitate the development of these conditions.

Patients and Methods

The characteristics of 953 patients diagnosed with CU in our Adult Allergy Clinic between January 1991 and June 2006 were retrospectively evaluated. The diagnosis of CU was based on patient history according to international guidelines or had been made in the same clinic in previous years [2]. NSAIDH, asthma and rhinitis as well as patient characteristics were evaluated. In the group of patients with available information on age at onset of urticaria, factors associated with the risk of asthma and rhinitis were evaluated, and in this group, NSAIDH was assessed as a possible risk factor for asthma and rhinitis. Patient characteristics and risk factors included nasal polyps, food allergy, metal sensitization, antibiotic hypersensitivity, smoking, familial history of allergic diseases and NSAIDH, dermatographism and having a pet. The familial history of allergic diseases and NSAIDH was retrieved from the patients charts.

The diagnosis of bronchial asthma was made by history according to international guidelines or had been made in the same clinic in previous years [12]. NSAIDH and antibiotic hypersensitivity were diagnosed previously by history and/or oral provocation test (OPT) [13]. Rhinitis was diagnosed by history and/or ENT examination, and nasal polyps were diagnosed by ENT examination only [14].

Routine skin prick tests were performed in all the patients except for patients who were pregnant, had acute urticaria and/or dermatographism or used antihistamines at the time of the study. Twelve standard antigen solutions (*Dermatophagoides pteronyssinus*, *Phleum pratense*, *Olea europaea*, *Artemisia vulgaris*, *Parietaria officinalis*, hazelnut, *Betula verrucosa*, cat, dog, horse, *Alternaria alternata* and *Cladosporium herbarum*) were used, which were prepared by ALK (Denmark) and Greer (USA). The standard antigen solutions were applied before pricking the skin on the volar aspect of the forearm with a special lancet having a 1-mm tip. Histamine and saline were used as positive and negative controls, respectively. A wheal with perpendicular diameters $\geq 3 \times 3$ mm was considered as a positive reaction. Atopy was defined as a positive reaction to any allergen [15]. A positive familial history of allergic diseases was considered when the patient reported a first-degree family member with the symptoms and/or diagnosis of asthma, allergic rhinitis and/or atopic dermatitis.

The CU group comprised patients with information on age at onset of urticaria, and – if present – asthma or rhinitis. Risk factors for the development of asthma and rhinitis were investigated among the patients with onset of asthma and or rhinitis after urticaria.

The drugs used for the management of CU were evaluated.

Associations between personal characteristics and risk factors for asthma and rhinitis were assessed using univariate and multivariate analyses, which were adjusted for age and gender. Frequencies were analyzed by χ^2 test and by Fisher's exact test with an expected frequency of 25% or more of the cells < 5 . As the age of the patients and age at onset of urticaria were normally distributed, these variables were compared with Student's *t* test. To compare multiple groups, one-way ANOVA was used. Logistic regression analysis was used to adjust associations which were statistically significant in univariate analysis for age and gender. Risk factors for the development of asthma and rhinitis in CU patients were assessed by Cox regression analysis adjusted for age at onset of urticaria and gender. Statistical significance was defined for $p < 0.05$.

Results

The distribution of the cases is shown in figure 1. Demographic data and clinical characteristics of the CU patients ($n = 953$), patients with a history of NSAIDH ($n = 236$), patients with NSAIDH detected by OPT ($n = 34$) and patients without NSAIDH ($n = 717$) are listed in table 1. A total of 261 OPTs were performed in 121 patients, and 47 tests were positive in 34 patients (tables 1, 2).

The prevalence rates of the drugs causing NSAIDH by history in the NSAID-intolerant group were 48.3, 32.4,

Table 1. Demographic data and clinical characteristics of the CU patients (total n = 953; NSAIDH history: n = 236; NSAIDH detected by OPTs: n = 34, and no NSAIDH history: n = 717)

	Total patients (n = 953)	CU with NSAIDH (n = 236)	CU with NSAIDH OPT+ (n = 34) ^b	CU without NSAIDH (n = 717)	p value ^c	p value ^d
Age, years	37.3 ± 12.2	39.0 ± 11.8	39.4 ± 10.7	36.7 ± 12.3	0.014	0.22
Female gender	665 (69.8%)	176 (74.6%)	24 (70.6%)	489 (68.2%)	0.06	0.76
Age at CU onset, years	32.3 ± 13.3	31.5 ± 12.9	33.8 ± 14.5	32.4 ± 13.3	0.45	0.74
Duration of symptoms, years	4.8 ± 7.2	5.7 ± 8.1	4.3 ± 7.0	4.6 ± 7.0	0.133	0.90
Asthma	98 (10.4%)	38 (16.4%)	4 (11.8%)	60 (8.4%)	<0.001	0.52
Age at asthma onset, years	28.5 ± 13.6	28.1 ± 12.2	27.7 ± 18.1	28.8 ± 14.7	0.824	0.89
Metal sensitization	139 (14.6%)	51 (21.6%)	8 (23.5%)	88 (12.3%)	<0.001	0.06
Antibiotic hypersensitivity	101 (10.6%)	49 (20.8%)	7 (20.6%)	52 (7.3%)	<0.001	0.01
Food allergy	174 (18.3%)	50 (21.2%)	1 (2.9%)	124 (17.3%)	0.18	0.03
Dermographism	261 (27.4%)	50 (21.2%)	4 (11.8%)	211 (29.4%)	0.01	0.02
Familial history of allergic diseases	389 (40.8%)	114 (48.3%)	11 (32.4%)	275 (38.4%)	0.007	0.48
History of familial NSAIDH	23 (2.4%)	19 (8%)	3 (8.8%)	4 (0.6%)	<0.001	0.003
Atopy ^a	114 (33.0%)	37 (38.5%)	5 (20.0%)	77 (30.9%)	0.18	<0.001
Rhinitis	185 (19.4%)	51 (21.4%)	5 (14.7%)	134 (18.7%)	0.34	0.56
Age at rhinitis onset, years	26.2 ± 11.3	26.3 ± 9.8	34.7 ± 7.0	26.2 ± 12.0	0.976	0.16
Nasal polyps	16 (1.7%)	10 (4.2%)	1 (2.9%)	6 (0.8%)	0.001	0.27
Smoking	370 (38.8%)	96 (40.7%)	10 (29.4%)	274 (38.2%)	0.50	0.29
Pet at home	121 (12.7%)	26 (11.0%)	1 (2.9%)	95 (13.2%)	0.37	0.11
Angioedema	304 (31.9%)	63 (26.7%)	4 (11.8%)	241 (33.6%)	0.04	0.008

^a Skin prick testing was performed in 345 of the patients. Positivity for aero- and food allergens was accepted as atopy. One hundred and three patients reacted positive to aeroallergens. In the OPT-positive group, skin prick tests with aero- and food allergens were performed in 25 patients.

^b OPTs were performed with any NSAID in 121 patients and were positive in 34.

^c Patients with CU and NSAIDH vs. patients with CU alone.

^d Patients with CU and OPT-positive NSAIDH vs. patients with CU alone.

22.3, 21.0, 1.3, 0.8, 15.5 and 6.3% for aspirin, metamizole, naproxen, paracetamol, meloxicam and nimesulide, undefined and other NSAIDs, respectively. There was history of hypersensitivity to more than one NSAID in 34.5% of the CU patients with NSAIDH. OPTs were performed with the aim of confirming NSAIDH in patients without a reliable history of at least two occasions reported or to provide a safe alternative in those with a reliable history. The responsible drugs, performed tests and results are shown in table 2.

Antibiotic hypersensitivity was diagnosed in 101 patients by history and/or drug provocation tests, and the spectrum was as follows: β -lactams 60%, trimethoprim sulfamethoxazole 25%, macrolides 6%, nitroimidazoles 4%, quinolones 3% and others 2%. The following reactions were noted: urticaria 65.1%, angioedema 45%, anaphylaxis 16.1%, others 14.5% and bronchospasm 5%. Safe alternative antibiotics were found by drug provocation tests for 25 patients who could not use any antibiotics.

In the treatment of CU, drugs were recorded in 339 patients: new generation antihistamines (92.9%), old generation antihistamines (37.8%), short- or long-term systemic steroids (28.9%), leukotriene antagonists (3.2%) and antidepressants (1.2%).

Associations between concomitant allergic diseases and patient characteristics are shown in table 3. Groups of CU and rhinitis (n = 125), CU and asthma (n = 40) and CU and both rhinitis and asthma (n = 58) were compared with the group with CU alone (n = 730).

The cases were also evaluated according to the age at onset of urticaria. Adjustments were made according to the age at onset of urticaria and gender, with age at urticaria onset being available in 777 patients. The two groups (urticaria onset age available vs. unavailable) were compared. Age and gender were not significantly different between both groups [mean age and (SD), 38.7 (12.2) and 36.9 years (12.2), p = 0.08, and female gender 72.7 and 69.1% in patients with age at CU onset available or un-

Table 2. Distribution of the NSAID-intolerant patients according to their history, the tests performed and the results of the tests

Drug	Test performed (n = 261)	Test+ (n = 47)	Reaction type, n
OPT with paracetamol	68	3	U:2, AN:1
History of paracetamol hypersensitivity (n = 51)	15	1	–
For confirmation of the suspected drug or safe alternative	53	2	–
OPT with acetylsalicylic acid	30	12	U:6, R:3, A:2, AN:1
History of acetylsalicylic acid hypersensitivity (n = 115)	12	7	–
For confirmation of the suspected drug or safe alternative	18	5	–
OPT with nimesulide	43	10	U:6, A:3, B:1
History of nimesulide hypersensitivity (n = 2)	1	1	–
For confirmation of the suspected drug or safe alternative	42	9	–
OPT with meloxicam	60	11	U:8, A:1, B:1, AN:1
History of meloxicam hypersensitivity (n = 3)	2	1	–
For confirmation of the suspected drug or safe alternative	58	10	–
OPT with metamizole	3	1	U:1
History of metamizole hypersensitivity (n = 77)	1	1	–
For confirmation of the suspected drug or safe alternative	2	–	–
OPT with naproxen sodium	7	4	U:3, A:1
History of naproxen sodium hypersensitivity (n = 53)	1	1	–
For confirmation of the suspected drug or safe alternative	6	3	–
OPT with rofecoxib	35	5	U:4, A:1
History of rofecoxib hypersensitivity (n = 1)	–	–	–
For confirmation of the suspected drug or safe alternative	35	5	–
OPT with celecoxib	15	1	U:1
History of celecoxib hypersensitivity (n = 1)	–	–	–
For confirmation of the suspected drug or safe alternative	15	1	–

U = Urticaria; A = angioedema; B = bronchospasm; AN = anaphylaxis; R = rhinitis.

known, respectively, $p = 0.35$]. Patients who did not report age at CU onset had a higher prevalence of metal sensitization (22.2 and 12.9%, respectively, $p = 0.002$), a familial history of allergic diseases (51.7 and 38.4%, respectively, $p = 0.001$), a familial history of NSAIDH (10.2 and 0.6%, respectively, $p < 0.001$), NSAIDH (64.8 and 15.7%, respectively, $p < 0.001$) and antibiotic hypersensitivity (18.2 and 8.9%, respectively, $p < 0.001$), but a lower prevalence of angioedema (13.1 and 36.2%, respectively, $p < 0.001$).

The group of patients with age at CU onset available was further subdivided according to the accompanying allergic disease. In patients who had asthma or rhinitis after CU, risk factors were analyzed. Table 4 shows univariate and Cox regression analyses of the factors associated with rhinitis and asthma after CU. Cox regression analysis was adjusted for age at CU onset and gender. In the CU-only group, 512 patients had no accompanying allergic disease, 45 had rhinitis, 12 had asthma and 9 had both rhinitis and asthma. Mean ages (SD) at CU onset

were 33.2 (12.8) for CU only, 26.2 (11.4) for CU and allergic rhinitis, 35.4 (17.8) for CU and asthma, and 29.6 (11.5) for CU concomitant with rhinitis and asthma. Median time intervals between the onset of CU and rhinitis were 0.7 and 0.5 years in the groups with rhinitis alone and rhinitis combined with asthma, respectively. Median intervals between the onset of CU and asthma were 0.6 and 0.25 years in the groups with asthma alone and rhinitis combined with asthma, respectively. Patients who developed both asthma and rhinitis were analyzed separately for each disease in Cox regression analysis. In the urticaria group, development of rhinitis was associated with angioedema (hazard ratio, HR: 0.4, 95% confidence interval, CI: 0.2–0.9), NSAIDH (HR: 5.2, 95% CI: 2.0–13.4) and atopy (HR: 5.2, 95% CI: 2.0–13.3). Development of asthma was associated with NSAIDH (HR: 52.9, 95% CI: 18.1–154.6) and atopy (HR: 16.6, 95% CI: 1.7–158.1).

Table 3. Association between concomitant allergic diseases (rhinitis and asthma) and patient characteristics

Patient characteristics	n	CU (n = 730)	CU + R (n = 125)	CU + A (n = 40)	CU + A + R (n = 58)	p value	CU + R (n = 125)	CU + A (n = 40)	CU + A + R (n = 58)
Age, years	953	37.6 (12.8)	34.9 (9.6)	41.0 (13.6)	35.9 (8.9)	0.02			
Female gender	665	67.4	74.6	72.5	86.4	0.01			
Smoking	370	40.6	36.5	27.5	30.5	0.16			
Familial history of allergic diseases	389	38.0	42.9	60.0	57.6	0.001	1.2 (0.8–1.7)	2.5 (1.3–4.9)	2.1 (1.2–3.6)
Familial history of NSAIDH	23	2.3	1.6	2.5	5.1	0.53			
Pet at home	121	11.8	14.4	15.0	19.0	0.37			
Dermographism	261	26.7	31.0	20.0	37.3	0.18			
Angioedema	304	35.6	24.6	17.5	13.6	<0.001	0.6 (9.4–0.9)	0.4 (0.2–0.9)	0.3 (0.1–0.6)
Food allergy	174	17.1	22.2	15.0	27.1	0.15			
Nasal polyps	16	0.1	4.0	0	18.6	<0.001	40.1 (4.6–355.4)	NA	191.0 (22.6–1,614.2)
NSAIDH	236	23.9	19.0	30.0	45.8	0.001	0.7 (0.4–1.2)	1.3 (0.7–2.7)	2.5 (1.4–4.4)
Antibiotic hypersensitivity	101	9.7	12.7	2.5	22.0	0.007	1.4 (0.8–2.5)	0.2 (0.03–1.6)	2.6 (1.3–5.2)
Metal sensitization	139	13.0	19.0	10.0	27.1	0.009	1.5 (0.9–2.4)	0.8 (0.3–2.3)	2.0 (1.1–3.9)
Atopy ^a	114	23.4	59.3	55.6	46.7	<0.001	4.0 (2.2–7.6)	4.9 (1.7–14.0)	2.7 (1.2–5.9)

Adjustments were made for age and gender in the logistic regression models. A = Asthma; NA = not assessed; R = rhinitis.

^a Skin prick testing was performed in 345 patients.

Table 4. Univariate and Cox regression analyses of the factors associated with rhinitis (R) and asthma (A) reported after urticaria (total n = 578)

Patient characteristics	n	CU only (n = 512)	CU then R (n = 45)	CU then A (n = 12)	CU then R + A (n = 9)	p – R	p – A	CU then R (n = 45) HR (95% CI)	CU then A (n = 12) HR (95% CI)
Age, years		37.2 (12.8)	34.0 (9.8)	40.5 (16.8)	34.9 (9.4)				
Female gender	391	66.4	77.8	66.7	88.9	0.04	0.35		
Smoking	229	41.2	24.4	33.3	33.3	0.03	0.47	0.6 (0.3–1.1)	0.7 (0.3–1.9)
Family history of allergic diseases	210	35.0	46.7	33.3	66.7	0.03	0.24	1.6 (0.9–2.7)	1.7 (0.7–4.0)
Family history of NSAIDH	2	0.2	0	0	0	1.00	1	NA	NA
Pet at home	75	11.9	22.2	25.0	11.1				
Dermographism	165	27.0	40.0	41.7	44.4	0.03	0.11	1.6 (0.9–2.8)	1.9 (0.8–4.5)
Angioedema	211	38.1	24.4	25.0	22.2	0.04	0.18	0.4 (0.2–0.9)	0.5 (0.2–1.3)
Food allergy	97	16.4	22.2	8.3	22.2	0.28	1	1.2 (0.6–2.2)	0.8 (0.2–2.8)
Nasal polyps	1	0	2.2	0	0	0.09	NA		
NSAIDH	9	0	8.9	25.0	22.2	<0.001	<0.001	5.2 (2.0–13.4)	52.9 (18.1–154.6)
Antibiotic hypersensitivity	37	6.8	4.4	0	0	0.56	0.39	0.4 (0.1–1.8)	NA
Metal sensitization	67	10.5	22.2	8.3	22.2	0.01	0.48	1.9 (1.0–3.6)	1.4 (0.4–4.7)
Atopy ^a	51	21.6	63.2	66.7	100	<0.001	0.01	5.2 (2.0–13.3)	16.6 (1.7–158.1)

Adjustments were made for age, age at onset of urticaria and gender in the Cox regression models. p – R = Urticaria and allergic rhinitis compared with urticaria; p – A = urticaria and asthma compared with urticaria.

^a Skin prick testing was performed in 186 patients.

Discussion

In this study, risk factors were evaluated in the patients with CU with or without other allergic diseases. The number of positive OPTs (47 tests positive in 34 of 261 tests performed in 121 patients) might seem low, but some of them were performed for confirmation in the ones who

did not have a reliable history and most of them with the aim of finding safe alternatives. Since OPT results are more appropriate for NSAIDH diagnosis, we compared this group with the group without NSAIDH. In addition, there is a female predominance in urticaria [4] which was also supported by this study.

NSAIDH may accompany many diseases and conditions including CU. Whereas in previous studies in NSAIDH patients a CU prevalence of 7–14% has been reported [13, 16–18], in our study almost 25% of the patients with CU had a history of NSAIDH. Although aspirin induces urticaria and/or angioedema in 0.07–0.2% of the general population, approximately one third of the patients with chronic idiopathic urticaria under remission experience an urticarial attack after using aspirin or NSAIDs and 70% of the patients with active disease have aggravation [4, 19–21]. In our CU patients, the prevalence of NSAIDH was close to that stated in the literature, with 22–26% of patients with chronic idiopathic urticaria having an exacerbation after aspirin challenge [22, 23]. In our study, 12% of all CU patients and 48.3% of CU patients with a history of NSAIDH presented with documented aspirin hypersensitivity. In another study, 30 of 74 CU patients with a history of aspirin sensitivity had positive reactions after aspirin challenge [24]. In our study, 7 of 12 patients with a history of aspirin sensitivity had positive aspirin challenge tests, possibly due to the increased sensitivity to NSAIDs in urticaria patients in remission. Since OPTs are performed in successfully treated patients, the test positivity rate might be lower.

In contrast to a previous study reporting that aspirin-induced CU patients were younger [25], our NSAID-intolerant CU patients were older than those without NSAIDH. The difference may be explained by a larger amount of lifelong NSAID consumption with increasing age, in agreement with our previous study [13]. When the ages of the groups were analyzed according to concomitant allergic diseases, patients with rhinitis were younger than patients with asthma with or without rhinitis.

An association between CU and bronchial hyperresponsiveness has been reported [26]. In a study of patients with both acute and chronic urticaria, 6.9% had asthma [4]. In our study, 10.4% of our CU patients had asthma. The asthma rate in our study group was higher than in the general population. CU was also found to be less common in NSAIDH patients with asthma compared to NSAIDH patients without asthma [13], being in contrast to another study [16]. In our study, the prevalence of asthma in CU patients with NSAIDH was significantly increased, and in patients with CU onset before asthma onset, CU patients had an increased risk of asthma. These data suggest that the coexistence of NSAIDH with CU might increase the risk of asthma, but further studies are needed to confirm these results.

The rhinitis rate was higher in our study compared to other studies [4, 27]. Although there were no significant differences between CU patients with and without NSAIDH, the coexistence of NSAIDH increased the risk of developing rhinitis if onset age of CU was before the onset age of rhinitis, in agreement with the results in asthma.

Nasal polyposis was a common finding in asthma and rhinitis patients in general. In our study, lower prevalence rates of nasal polyposis had been observed in CU patients without concomitant diseases. If there were other accompanying diseases, the prevalence of nasal polyposis was higher.

CU may occur in non-atopic individuals and in the patients with a personal or familial history of allergic diseases, including asthma, rhinitis and eczema. The percentages for a familial history of allergic diseases were 24 and 35% in two other studies in CU patients [4, 27]. Our rate of 40.8% exceeded those of the other series, but familial urticaria was also included in this patient group. Another study showed that a familial history of allergic diseases was significantly higher in asthma with NSAIDH than without NSAIDH [13]. In our study, the coexistence of NSAIDH increased the prevalence of a familial history of allergic diseases to 48.3%, being significantly higher compared with those without NSAIDH. The familial history of allergic diseases also increased in CU patients with concomitant allergic disease. All these data confirm that all of these allergic conditions may have a genetic background.

A familial history of NSAIDH was noted in 0.6 and 8% of our CU patients without and with NSAIDH, respectively. The prevalence of a history of familial NSAIDH was previously suggested to be 9.7% in all NSAIDH patients [18]. One of our previous surveys showed that 7.3–10.5% of NSAIDH patients had a history of familial NSAIDH in the presence of comorbidities [16]. In a recent survey, aspirin-induced urticaria was more frequent in two families inheriting the leukotriene C₄ synthase –444C allele, but future studies have to confirm these findings in a larger patient cohort [28]. All these data suggested a genetic background in NSAIDH and urticaria.

Although allergens may cause contact urticaria, anaphylaxis and in some cases acute urticaria by cross-linking of specific IgE on mast cells and basophils, immediate hypersensitivity reactions are hardly ever the cause of chronic urticaria [29]. A study disclosed 8% IgE-mediated type I allergic reactions in urticaria patients [4]. The prevalence of atopy determined by skin prick test was

33% in our study, and although there was no significant difference between CU patients with and without NSAIDH, the rate was significantly lower in OPT-positive patients than in those without NSAIDH. This is an interesting finding which is not easy to explain. In our study, atopy was more frequent in asthma and rhinitis, and the presence of atopy increased the development of asthma and rhinitis in CU patients. Skin prick tests were apparently only performed in a relatively small number of patients (n = 114), because we have performed these tests to patients with suspected IgE-mediated disease and not the unwanted conditions mentioned in Patients and Methods.

Anaphylaxis is a serious allergic reaction that may cause death. In our study, totally 13 patients had a history of anaphylaxis and 4.2% of all patients had a history of NSAIDH; CU patients with NSAIDH had an increased risk of anaphylaxis.

Angioedema may occur concomitantly in nearly half of the CU patients [30]. In our study, approximately 32% had angioedema with or without urticaria. Our results were higher than those of other studies, but below the general incidence [4, 30]. This may be explained by the inclusion of all of our angioedema cases with or without wheals. Our results also showed that the coexistence of angioedema decreased the risk of developing rhinitis in urticaria patients.

The incidence of antibiotic hypersensitivity was decreased in our study compared to another survey including patients with acute and chronic urticaria [4]. Antibiotic hypersensitivity was significantly more common in CU patients with NSAIDH, asthma or rhinitis compared to those without NSAIDH in our study. Previously, a higher prevalence of antibiotic hypersensitivity was noted in the presence of NSAIDH [13, 16].

A history of metal sensitization was found in 14.6% of all CU patients in our study. Patients with NSAIDH, asthma and rhinitis had significantly more often a history of metal sensitization in our study. It has been shown earlier that metal sensitization is more frequent in NSAIDH patients [13]. Two other studies showed higher rates of metal sensitization by patch test in CU and asthma patients [31, 32]. The significantly lower rate of food allergy in OPT-positive patients compared to the group without an NSAIDH history is also interesting.

In conclusion, asthma, nasal polyps, antibiotic hypersensitivity, metal sensitization and a history of familial NSAIDH are more frequent in CU patients with NSAIDH compared to those without NSAIDH. CU may accompany many other potentially immunomediated diseases and the coexistence of NSAIDH and CU may increase the risk of developing asthma and rhinitis.

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