

ORIGINAL ARTICLE

EXPERIMENTAL ALLERGY AND IMMUNOLOGY

NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study

I. Doña¹, N. Blanca-López², M. J. Torres¹, F. Gómez¹, J. Fernández³, M. A. Zambonino¹,
F. J. Monteseirín⁴, G. Canto², M. Blanca¹ & J. A. Cornejo-García⁵

¹Allergy Service, Carlos Haya Hospital, Malaga; ²Allergy Service, Infanta Leonor Hospital, Madrid; ³Allergy Service, Elche General Hospital, Alicante; ⁴Allergy Service, Virgen Macarena Hospital, Sevilla; ⁵Research Laboratory for Allergic Diseases, Carlos Haya Hospital, Malaga, Spain

To cite this article: Doña I, Blanca-López N, Torres MJ, Gómez F, Fernández J, Zambonino MA, Monteseirín FJ, Canto G, Blanca M, Cornejo-García JA. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. *Allergy* 2013; DOI: 10.1111/all.12335.

Keywords

atopy; chronic urticaria; hypersensitivity; nonsteroidal anti-inflammatory drugs; NSAID-induced urticaria/angioedema.

Correspondence

Inmaculada Doña, Allergy Service, pabellón 6, primera planta, Carlos Haya Hospital (Pabellón C), Plaza del Hospital Civil, 29009 Malaga, Spain.

Tel.: +34 951290346

Fax: +34 951290302

E-mail: inmadd@hotmail.com

Accepted for publication 24 October 2013

DOI:10.1111/all.12335

Edited by: Pascal Demoly

Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequent medicaments involved in drug hypersensitivity reactions, with NSAID-induced urticaria/angioedema (NIUA) being the most frequent clinical entity. The natural evolution of NIUA has been suggested to lead to chronic urticaria (CU) in an important proportion of patients, such that NIUA may therefore precede CU. Our aim was to verify whether these entities are related by following up a large cohort of patients with NIUA as well as a control group over a long period of time.

Methods: The study comprised three groups: (i) patients with a confirmed history of NIUA (more than two episodes with at least two different NSAIDs or positive drug provocation tests), (ii) patients with more than two episodes of urticaria/angioedema to a single NSAID with good tolerance to a strong COX-1 inhibitor and/or evidence by *in vivo* tests supporting specific IgE antibodies to the drug (single NSAID-induced urticaria/angioedema, SNIUA), and (iii) controls who tolerated NSAIDs. All cases in the three groups were followed up over a period of 12 years.

Results: There were 190 patients with NIUA (64.6% female; mean age 43.71 ± 15.82 years, 110 with SNIUA, and 152 controls. At the 12-year evaluation, 12 patients with NIUA (6.15%) had developed CU over a 1- to 8-year period. Similar proportions were seen in SNIUA and controls.

Conclusions: Nonsteroidal anti-inflammatory drugs-induced urticaria/angioedema does not seem to precede the onset of CU over the medium term. Further research including a longer follow-up is necessary to verify this observation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequent medicaments involved in drug hypersensitivity reactions (DHR) (1–3), particularly in Spain, where they are the most frequent medicaments implicated (4). Although several clinical entities can be seen, there are basically two types of reactions, the most common being nonim-

munologically mediated reactions (cross-reactive) (5–7). The other type involves a response immunologically mediated that is induced by a single drug, but the patients have good tolerance to other chemically unrelated compounds (non-cross-reactive) (7–11). Cross-reactivity to NSAIDs may affect the skin and/or the respiratory airways (7, 12–14), although the skin is more commonly affected (5). Three types of cutaneous entities have been described after NSAID intake: acute urticaria/angioedema in the absence of any history indicative of chronic urticaria (CU), called NSAID-induced urticaria/angioedema (NIUA); the re-aggravation of pre-existing idiopathic CU, called NSAID-exacerbated cutaneous disease;

Abbreviations

CU, chronic urticaria; DPT, drug provocation test; NIUA, NSAID-induced urticaria/angioedema; NSAIDs, nonsteroidal anti-inflammatory drugs; SNIUA, single NSAID-induced urticaria/angioedema.

and immediate urticaria/angioedema induced by a single NSAID with good tolerance to other chemically nonrelated NSAIDs and no history of CU or asthma, called single NSAID-induced urticaria/angioedema (SNIUA) (7, 15).

Chronic urticaria has a variable clinical course, and the responsiveness to NSAIDs may fluctuate depending on the disease activity, being greater when the disease is active and less frequent when CU is under control (14, 16, 17). In fact, from 21% to 30% of patients with CU may develop skin symptoms after the intake of a NSAID (16). Whether NIUA is a separate individual entity or whether it may evolve to CU in its natural course is not firmly established. Up to one in three patients with NIUA may develop CU over time, and it has been suggested that NIUA may therefore precede CU (18).

The aim of this study was to verify this observation by following up a large cohort of well-characterized patients with NIUA over a long period of time to establish the relationship between these two entities.

Methods

First evaluation

We evaluated patients aged 14–80 years with cutaneous symptoms suggestive of hypersensitivity reactions to one or more NSAIDs who attended for the first time at our allergology department during January–December 2000.

The patients were classified, as previously described (5), into two groups: those who experienced more than two episodes of urticaria/angioedema after the intake of at least two different NSAIDs or with a positive drug provocation test (DPT) were classified as having NIUA; and patients who had at least two episodes of urticaria/angioedema with the same NSAID and good tolerance to a strong COX-1 inhibitor and/or evidence by *in vivo* tests supporting specific IgE antibodies to the drug were classified as having a single NSAID-induced urticaria/angioedema (SNIUA). A further control group of persons with no history of CU and good tolerance to aspirin and other NSAIDs confirmed by DPT was also included. The procedures and doses used to carry out the challenges as well as the skin tests with NSAIDs have been described in detail previously (5). Chronic urticaria was defined as the spontaneous recurrence of hives with or without angioedema lasting more than 6 weeks.

Exclusion criteria were patients younger than 14 and older than 80 years of age; patients with a suspicion or evidence of hypersensitivity reactions such as fixed drug eruption, erythema multiforme, Stevens–Johnson–TEN complex, or acute exanthematic pustulosis; patients with CU or acute recurrent urticaria not attributed to NSAID intake; pregnant or breastfeeding patients; patients taking beta-blockers or ACE inhibitors or with contraindications for epinephrine administration; patients who had acute infections and/or underlying cardiac, hepatic, or renal diseases that contraindicated DPT; subjects with psychosomatic disorders; and patients with one or more reactions to one NSAID with unknown tolerance to others.

A clinical questionnaire was given including questions on urticaria and/or angioedema (localization of hives, duration,

NSAID involved, and other triggers such as foods, infections, stress, other drugs, and physical stimulus); nasal and bronchial symptoms (sneezing, itching, watery nose, nasal blockage, difficulty breathing, cough, and wheezing); and symptoms attributed to food, such as oral allergy syndrome, eczema, anaphylaxis, or shock.

In all the study patients, the atopy status was assessed with a skin prick test performed with a battery of 30 common inhalant allergens, including pollens, house dust mites, molds, and animal danders (ALK, Madrid, Spain). Histamine hydrochloride 10 mg/ml and phenolated glycerol–saline were used as positive and negative controls, respectively. A positive skin prick test response was defined as a wheal diameter of 3 mm or larger to at least one of these aeroallergens. The patients were requested to stop taking any medications that contained antihistamine at least 8 days before skin testing. If patients had a history compatible with food allergy, skin prick test was also performed with a battery of 12 common food allergens that included animal, fruit, and vegetable allergens. These were shrimp, apple, melon, peach, banana, peanut, almond, hazelnut, walnut, sunflower seed, lentil, and mustard, provided by ALK.

Follow-up evaluation

All the cases were prospectively re-evaluated every 3 years over a 12-year period, giving a total of four re-evaluations (2003, 2006, 2009, and 2012). At each visit, the same questionnaire as used at baseline was given, and the atopy status was assessed with a skin prick test performed with the same battery of allergens as used at the first evaluation.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethics Committees of Carlos Haya hospital. All the participants were informed orally about the study and signed the corresponding informed consent.

Statistical analysis

Descriptive statistics (frequency, mean, median, SD, and range) were used to study the population. Chi-square analysis was used to test differences for nominal variables and the Fisher's test when there were no criteria for using the chi-square test. The ANOVA test was used for quantitative variables. All reported *P* values represented two-tailed tests, with values <0.05 considered significant. Kaplan–Meier analysis was performed with the time to the appearance of CU after starting the follow-up period.

Results

First evaluation

A total of 505 patients were evaluated at their first visit during 2000, although only 452 were finally included: 190 were confirmed as having NIUA, 110 as having SNIUA, and there were 152 controls. A total of 30 NIUA, 11 SNIUA, and 12 controls were excluded because they did not attend all the

follow-up visits. The clinical details of the patients finally included in each group are summarized in Table 1; 64.6% were female, and the mean age was 43.71 ± 15.82 years. No differences in gender or age were found between the three groups (Table 1).

The analysis of the time interval between the first reaction to a NSAID as reported by the patient and the first evaluation showed no differences between patients with NIUA and SNIUA (87.24 ± 84.44 (3–300) vs 122 ± 106.71 (6–216) months).

Concerning the drugs inducing the episodes, in 35.2% of the group of patients with NIUA, the reaction was induced by propionic acid derivatives (basically ibuprofen), followed by aspirin (23.04%) and pyrazolones (mainly dipyron; 16.4%). Arylacetic acid derivatives (basically diclofenac) induced the response in 11.9% and paracetamol in 10.1%. In patients with SNIUA, propionic acid derivatives (mainly ibuprofen) were the most frequent drugs involved (36.4%; $P = 0.808$), together with pyrazolones (basically dipyron; 36.4%; $P < 0.0001$) followed by arylacetic acid derivatives (diclofenac) and paracetamol (both 9.1%; Table 2).

The time interval between drug administration and symptom appearance is shown in Table 3. Most of the patients with NIUA and SNIUA experienced the episode within 1 h of drug administration, while 20% had the reaction within 1–6 h. Only a very few cases with NIUA experienced their reaction after more than 6 h ($P < 0.005$). Because a very low number of patients did not specify the time interval between drug intake and appearance of the symptoms, this was not compared.

After skin testing, 107 (56.31%) patients with NIUA were considered to be atopic, with significant differences compared with patients with SNIUA and controls, where 44 (40%) and 62 (40.78%) were atopic, respectively ($P < 0.009$).

In patients with NIUA, the most significant association was detected with positive skin prick testing to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and dog and cat

Table 2 Drugs involved in NSAID-induced reactions reported by patients with NIUA and SNIUA

Drugs involved (%)	NIUA	SNIUA	P
Aspirin	23.04	0	0.0001
Indoleacetic acid (indomethacin)	0.46	0	1.00
Nicotinic acid (lysine clonixinate)	1.38	0	0.351
Arylacetic acid	11.9	9.1	0.379
Diclofenac	11.5	9.1	0.516
Aceclofenac	0.4	0	1.00
Propionic acid	35.2	36.4	0.808
Ibuprofen	29.6	36.4	0.156
Naproxen	2	0	0.216
Dexketoprofen	2.7	0	0.08
Ketorolac	0.9	0	0.584
Pyrazolone	16.4	36.4	0.0001
Dipyron	15.5	18.2	0.487
Propyphenazone	0.9	18.2	0.0001
Oxicam	1.84	0	0.089
Piroxicam	1.3	0	0.351
Meloxicam	0.4	0	1.00
Paracetamol	10.1	9.1	0.831
Selective COX-2 inhibitor (etoricoxib)	0.4	0	1.00

NIUA, NSAID-induced urticaria/angioedema; SNIUA, single NSAID-induced urticaria/angioedema.

dander (Table 1). No differences were found in the prevalence for pollen allergens (*Lolium* and *Olea*) or molds (*Alternaria*). Comparison of the clinical entities in the three groups showed a higher percentage of asthma in patients with NIUA and SNIUA compared with controls (7.36% and 8.18%, respectively, compared with 1.97%; $P < 0.001$; Table 1).

No differences were found in the percentage of food allergy comparing the three groups. In the group of patients with NIUA, a total of 16 patients were positive to at least one food allergen: nine were positive to apple, eight to

Table 1 Clinical features of the study population

	NIUA (n = 190)	SNIUA (n = 110)	Controls (n = 152)	P
Age (years)	38.79 ± 14.43 (14–71)	39.36 ± 11.09 (17–56)	40.7 ± 14.7 (14–80)	0.698
Gender n (%) M/ n (%) F	68 (35.75)/122 (64.21)	40 (36.36)/70 (63.63)	51 (33.55)/101 (66.44)	0.918
Atopy n (%)	107 (56.31)	44 (40)	62 (40.78)	0.009
Positive skin prick tests to common aeroallergens n (%):				
Lolium	28 (14.73)	18 (16.36)	27 (17.76)	0.274
Cupressus	16 (8.42)	5 (4.54)	4 (2.63)	0.344
Olea	46 (24.21)	15 (13.63)	26 (17.1)	0.055
<i>Dermatophagoides pteronyssinus</i>	66 (34.71)	19 (17.27)	32 (21.05)	0.012
<i>Dermatophagoides farinae</i>	62 (32.63)	10 (9.09)	30 (19.73)	0.0001
<i>Alternaria</i>	10 (5.26)	1 (0.90)	2 (1.31)	0.104
Dog dander	26 (13.68)	3 (2.72)	6 (3.94)	0.002
Cat dander	30 (15.78)	4 (3.63)	13 (8.55)	0.002
Clinical entities n (%):				
Rhinitis	52 (27.36)	25 (22.72)	32 (21.05)	0.838
Asthma	14 (7.36)	9 (8.18)	3 (1.97)	0.01
Food allergy	16 (8.42)	5 (4.54)	8 (5.26)	0.768

NSAID, Nonsteroidal anti-inflammatory drugs; NIUA, NSAID-induced urticaria/angioedema; SNIUA, single NSAID-induced urticaria/angioedema.

Table 3 Time interval between drug administration and appearance of reaction according to the patient in NIUA and SNIUA

Time interval	NIUA (%)	SNIUA (%)	<i>P</i>
<1 h	53.68	54.54	0.885
1–6 h	23.15	18.18	0.311
6–24 h	6.31	0	0.005
Not recorded	16.84	27.27	Not done

NIUA, NSAID-induced urticaria/angioedema; SNIUA, single NSAID-induced urticaria/angioedema.

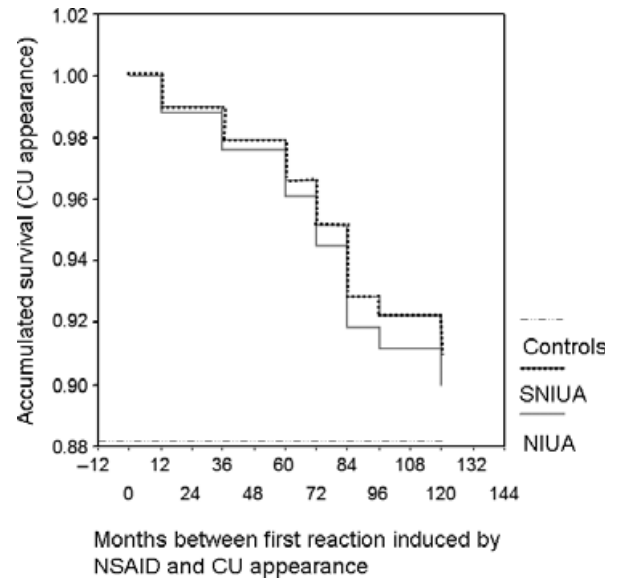
melon, ten to peach, two to banana, three to peanut, three to almond, two to hazelnut, two to walnut, two to sunflower seed, two to lentil, one to mustard, and seven to shrimp. In the group of patients with SNIUA, a total of five patients were positive to at least one food allergen: five to peach, four to melon, and one to peanut. In the control group, a total of eight patients were positive to at least one food allergen: eight to peach, seven to melon, and three to peanut.

Follow-up visit

All the study cases were re-evaluated four times during the 12-year period (2003, 2006, 2009, and 2012).

CU development

During the follow-up period, a total of 27 (6.04%) patients developed CU. The percentage of those who developed CU was similar in the three groups: 12 (6.31%) patients with NIUA, 6 (5.45%) patients with SNIUA, and 9 (5.92%) controls. The differences were not significant. No statistical association was found between the type of NSAID hypersensitivity reaction (NIUA and SNIUA) and the development of CU (OR: 0.856; 95% CI (0.312–2.348); *P* = 0.762). Patients with NIUA developed CU 62.27 ± 27.94 (12–96) months after the first NSAID-induced reaction: two patients developed CU after 12 months, one after 36 months, two after 60 months, three after 72 months, three after 84 months, and

**Figure 1** Comparison of the time to appearance of chronic urticaria in patients with Nonsteroidal anti-inflammatory drugs-induced urticaria/angioedema and single NSAID-induced urticaria/angioedema (Kaplan–Meier analysis).

one after 96 months. Patients with SNIUA developed CU 58 ± 39 (12–120) months after the first NSAID-induced reaction: one patient after 12 months, two after 36 months, one after 60 months, one after 84 months, and one after 120 months (Table 4). Comparison between patients with NIUA and SNIUA showed no significant differences in the time interval between the first NSAID-induced reaction and the appearance of CU (Fig. 1) or in the time interval between the first NSAID-induced reaction and the last follow-up visit in 2012 (215.14 ± 87.18 (128–424) vs 244 ± 109.98 (134–340) months).

Comparison of the patients with NIUA who developed CU and those who did not showed that the time interval

Table 4 Clinical features of the patients re-evaluated during the follow-up period

	NIUA	SNIUA	Controls	<i>P</i>
Patients who developed atopy during the follow-up period, <i>n</i> (%)	2 (1.05)	0	0	0.160
Patients who developed chronic urticaria (CU) during the follow-up period, <i>n</i> (%)	12 (6.31)	6 (5.45)	9 (5.92)	0.804
Time interval between first NSAID-induced reaction and CU onset, months $\pm$ SD (range)	62.27 ± 27.94 (12–96)	58 ± 39 (12–120)	NA	0.713
12 months	2	1	NA	
36 months	1	2	NA	
60 months	2	1	NA	
72 months	3	0	NA	
84 months	3	1	NA	
96 months	1	0	NA	
120 months	0	1	NA	

NA, not applicable; SNIUA, single NSAID-induced urticaria/angioedema.

Table 5 Clinical features of the patients who developed CU

Patient number	Group	Age	Gender	Rhinitis	Asthma	Food allergy	Drug involved	Drug tolerated	First NSAID-induced reaction	CU onset	Atopy	Positive inhalant allergens in skin prick test
1	NIUA	63	Male	No	No	No	Ibuprofen/Dipyrrone	Piroxicam/Paracetamol	1999	2000	No	—
2	NIUA	56	Female	No	No	No	Ibuprofen/Diclofenac	Paracetamol	2000	2000	No	—
3	NIUA	32	Female	No	Yes	No	Ibuprofen/aspirin	Paracetamol/Piroxicam	1999	2004	Yes	Dog dander/Cat dander/Latex
4	NIUA	20	Male	Yes	No	Yes	Ibuprofen/Diclofenac/Dipyrrone	Etoricoxib	1998	2005	Yes	Parietaria/Dp/Df/Dog dander/Cat dander
5	NIUA	56	Female	Yes	No	No	Ibuprofen/Paracetamol	Dipyrrone/Paracetamol	1997	2003	No	—
6	NIUA	42	Female	No	No	No	Ibuprofen/Paracetamol	Etoricoxib	2000	2003	No	—
7	NIUA	18	Male	No	Yes	Yes	Ibuprofen/Diclofenac/Dipyrrone	Etoricoxib	1997	2002	Yes	Parietaria/Dog dander
8	NIUA	55	Male	No	No	No	Ibuprofen/Diclofenac	Piroxicam/Paracetamol	1995	2002	No	—
9	NIUA	54	Female	Yes	No	No	Ibuprofen/Paracetamol	Dipyrrone/Paracetamol	1999	2000	No	—
10	NIUA	40	Female	No	No	No	Ibuprofen/aspirin	Paracetamol	1997	2004	Yes	Dp/Df/Cat dander
11	NIUA	41	Female	No	No	No	Ibuprofen/Paracetamol	Etoricoxib	1996	2003	No	—
12	NIUA	60	Female	Yes	No	No	Ibuprofen/Dipyrrone	Paracetamol	1997	2005	No	—
13	SNIUA	28	Female	No	No	No	Ibuprofen	Aspirin	2000	2001	No	—
14	SNIUA	28	Female	No	No	No	Ibuprofen	Aspirin	1998	2001	No	—
15	SNIUA	17	Female	No	No	No	Ibuprofen	Aspirin	1999	2002	No	—
16	SNIUA	49	Male	No	No	No	Dipyrrone	Diclofenac	1998	2005	No	—
17	SNIUA	43	Female	No	No	No	Dipyrrone	Aspirin	1997	2007	No	—
18	SNIUA	41	Female	No	No	No	Diclofenac	Aspirin	1996	2001	No	—
19	Control	40	Male	No	No	No	NA	NA	NA	2011	No	—
20	Control	45	Female	No	No	No	NA	NA	NA	2010	No	—
21	Control	51	Female	No	No	No	NA	NA	NA	2012	No	—
22	Control	39	Female	No	No	No	NA	NA	NA	2012	No	—
23	Control	58	Female	No	No	No	NA	NA	NA	2008	No	—
24	Control	38	Female	No	No	No	NA	NA	NA	2010	No	—
25	Control	43	Male	No	No	No	NA	NA	NA	2009	No	—
26	Control	56	Female	No	No	No	NA	NA	NA	2011	No	—
27	Control	52	Female	No	No	No	NA	NA	NA	2012	No	—

CU, chronic urticaria; NIUA, NSAID-induced urticaria/angioedema; SNIUA, single NSAID-induced urticaria/angioedema.

between the first NSAID-induced reaction and the last follow-up visit in 2012 was longer in those who did not develop CU (228.60 ± 87.96 months vs 156 ± 24.80 months; $P < 0.002$). From the total number of cases who abandoned the follow-up period, 12 cases abandoned after 6 years without any evidence of developing CU. The other four died of another process not related to CU, and the remaining was no longer allocated (Table 5).

Atopy status

Two patients with NIUA and negative skin prick tests at the first visit developed positive skin prick tests during the follow-up period: one patient developed positivity to *D. farinae* and had rhinitis in 2006 and one patient developed positivity to *Alternaria* in 2009, but had no respiratory symptoms. All patients with SNIUA and controls with negative skin prick tests at the first visit continued to be negative at the follow-up evaluations.

Discussion

Nonsteroidal anti-inflammatory drugs are the most frequent medicaments involved in drug hypersensitivity reactions (4), with NIUA being the most frequent clinical entity (4, 5). However, most studies on skin reactions induced by cross-reactivity to NSAIDs have focused on reactivation of pre-existing CU after intake of these drugs. NSAIDs exacerbate not only idiopathic CU (19), but also other types of urticaria, for example, cholinergic, types of physical urticaria, and exercise-induced urticaria (20–22). NIUA has been considered an entity that evolves to CU in many patients (18). Evidence indicates that the underlying mechanism of the reactivation of pre-existing CU after NSAID intake is related to COX-1 inhibition, similar to aspirin-induced asthma (23). This explains the response to various COX-1 inhibitors with different chemical structures. Eicosanoid alterations with an increase in cysteinyl leukotriene and prostaglandin D2 levels after aspirin challenge were reported in these patients (17, 23). This mechanism has also been suggested for NIUA (14, 17, 24).

However, CU has a variable clinical course, and the responsiveness to NSAIDs may show temporary fluctuations depending on the activity of the underlying chronic disease, being greater when the disease is active and less frequent when CU is under control (14, 16, 17). From 21% to 30% of patients with CU may develop cutaneous symptoms after the intake of a NSAID (16, 19), and a large percentage of these patients may later tolerate NSAIDs after the CU disappears (14, 17). The mechanism involved in the urticarial eruption seems to correlate well with the clinical status of the patient (17).

Whether NIUA is a separate entity or whether it may evolve to CU in its natural course has not been appropriately addressed. Asero evaluated a group of 121 patients with NIUA over a variable period of 1–10 years after their first visit, estimating that 30% of patients developed urticaria in the absence of any trigger (18). However, no control group with good tolerance to NSAIDs was evaluated. In our study, we followed up 190 patients with a confirmed history of

NIUA over a 12-year period, detecting 12 patients (6.15%) who developed CU during the follow-up period. Similar proportions were found in SNIUA and in controls. More studies are needed to verify these findings, however.

Recent years have seen increasing interest in the precise phenotyping of different clinical entities related with drug allergy, with the idea of undertaking pharmacogenetics studies (25). These studies are of particular interest in NIUA (24), as it has been shown to be the most common manifestation induced by these drugs. Therefore, whether NIUA is a separate entity or whether it may evolve to CU has to be established as a critical step to define this entity.

Nonsteroidal anti-inflammatory drugs-induced urticaria/angioedema is more frequent in atopic patients (5, 26–28), particularly in some countries that have a high prevalence of house dust mite sensitization (27, 29). In our study, the percentage of atopy was higher in patients with NIUA compared with SNIUA and controls (56% vs 40%), and the most significant association was with house dust mites. Similar results have been reported previously (5). A high percentage of patients with CU (30) show mugwort sensitization, although in our population was to house dust mite, not to pollen. In the natural evolution, we found no increase in the percentage of atopic patients. The LTC4S gene is in the same chromosomal region as genes implicated in atopy, including IL-4, IL-5, and IL-13. CysLTs have been shown to enhance the production of IgE and IgG antibodies by B lymphocytes (31–33). As the mechanism determining the association between NSAID intolerance and atopy is currently unknown, increasing interest is being shown in performing genetic studies to attempt to clarify the role of atopy in NSAID hypersensitivity (34).

Summarizing, we conclude that NIUA does not generally evolve to CU and that the proportion of NIUA patients who develop CU is similar to those with SNIUA or controls who develop CU. These data support the idea that NIUA is a well-defined and consistent entity. Further studies are needed to understand the pathomechanisms of NIUA to identify genes involved in susceptibility to this entity.

Acknowledgments

We thank Ian Johnstone for help with the final English language version of the manuscript.

Conflicts of interest

None of the authors has any conflict of interest, nor have they received any money for this study. Research is part of their daily activities. All the authors had full access to all the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. This study was supported by grants from Carlos III National Health Institute RD12/0013/0001 (RIRAAF network), PI12/02247, PI071220, PI10/01598, and from the Health Government of Andalucía, PI-0279-2012. Dr. Cornejo-García is a postdoctoral researcher of the Juan de la Cierva Program (Spanish Ministry of Science and Innovation).

References

- Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004;**34**:1597–1601.
- Messaad D, Sahla H, Benahmed S, Goudard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;**140**:1001–1006.
- Chen CJ, Cheng CF, Lin HY, Hung SP, Chen WC, Lin MS. A comprehensive 4-year survey of adverse drug reactions using a network-based hospital system. *J Clin Pharm Ther* 2012;**37**:647–651.
- Doña I, Blanca-López N, Torres MJ, García-Campos J, García-Núñez I, Gómez F et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol* 2012;**22**:363–371.
- Doña I, Blanca-Lopez N, Cornejo-Garcia JA, Torres MJ, Laguna JJ, Fernandez J et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011;**41**:86–95.
- Szczeklik A, Nizankowska E, Sanak M. Hypersensitivity to aspirin and non-steroidal antiinflammatory drugs. In: Adkinson NF, Bochner BS, Busse WW, Holgate S, Lemanske RF, Simons FE, editors. *Middleton's Allergy, principles and practice*, 7th edn. Philadelphia: Mosby, 2009:1227–1243.
- Kowalski M, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs). *Allergy* 2013;**68**:1219–1232.
- Himly M, Jahn-Schmid B, Pitterschatzsch K, Bohle B, Grubmayr K, Ferreira F et al. IgE-mediated immediate type hypersensitivity to the pyrazolone drug propyphenazone. *J Allergy Clin Immunol* 2003;**111**:882–888.
- Schneider CH, Kasper MF, de Weck AL, Rolli H, Angst BD. Diagnosis of antibody-mediated drug allergy. Pyrazolinone and pyrazolidinedione cross-reactivity relationships. *Allergy* 1987;**42**:597–603.
- Blanca M, Perez E, Garcia JJ, Miranda A, Terrados S, Vega JM et al. Angioedema and IgE antibodies to aspirin: a case report. *Ann Allergy* 1989;**62**:295–298.
- Canto MG, Andreu I, Fernandez J, Blanca M. Selective immediate hypersensitivity reactions to NSAIDs. *Curr Opin Allergy Clin Immunol* 2009;**9**:293–297.
- Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol* 2003;**111**:913–921.
- Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 2006;**118**:773–786.
- Sánchez-Borges M. NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). *Med Clin North Am* 2010;**94**:853–864.
- Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. *Allergy* 2011;**66**:818–829.
- Asero R. Multiple sensitivity to NSAID. *Allergy* 2000;**55**:893–894.
- Setkowicz M, Mastalerz L, Podolec-Rubis M, Sanak M, Szczeklik A. Clinical course and urinary eicosanoids in patients with aspirin-induced urticaria followed up for 4 years. *J Allergy Clin Immunol* 2009;**123**:174–178.
- Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. *J Allergy Clin Immunol* 2003;**111**:1095–1098.
- Comert S, Celebioglu E, Karakaya G, Kalayoncu AF. The general characteristics of acute urticaria attacks and the factors predictive of progression to chronic urticaria. *Allergol Immunopathol (Madr)* 2013;**41**:239–245.
- Izumi K, Aihara M, Ikezawa Z. Effects of non steroidal antiinflammatory drugs (NSAIDs) on immediate-type food allergy analysis of Japanese cases from 1998 to 2009. *Arerugi* 2009;**58**:1629–1639.
- Suzuki Y, Ra C. Analysis of the mechanism for the development of allergic skin inflammation and the application for its treatment: aspirin modulation of IgE-dependent mast cell activation: role of aspirin-induced exacerbation of immediate allergy. *J Pharmacol Sci* 2009;**110**:237–244.
- Morita E, Kunie K, Matsuo H. Food-dependent exercise-induced anaphylaxis. *J Dermatol Sci* 2007;**47**:109–117.
- Mastalerz L, Setkowicz M, Sanak M, Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol* 2004;**113**:771–775.
- Cornejo-García JA, Jagemann LR, Blanca-López N, Doña I, Flores C, Guéant-Rodríguez RM et al. Genetic variants of the arachidonic acid pathway in non-steroidal anti-inflammatory drug-induced acute urticaria. *Clin Exp Allergy* 2012;**42**:1772–1781.
- Houle D, Govindaraju DR, Omholt S. Phenomics: the next challenge. *Nat Rev Genet* 2010;**11**:855–866.
- Quirarte J, Blanco C, Castillo R, Delgado J, Carrillo T. Intolerance to nonsteroidal anti-inflammatory drugs: results of controlled drug challenges in 98 patients. *J Allergy Clin Immunol* 1996;**98**:678–685.
- Sanchez-Borges M, Acevedo N, Caraballo L, Capriles-Hulett A, Caballero-Fonseca F. Increased total and mite-specific immunoglobulin E in patients with aspirin-induced urticaria and angioedema. *J Investig Allergol Clin Immunol* 2010;**20**:139–145.
- Kim HA, Ye YM, Kim SH, Hur GY, Park HS. Association of beta 2-adrenergic receptor polymorphism with the phenotype of aspirin-intolerant acute urticaria. *Yonsei Med J* 2007;**48**:1079–1081.
- Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000;**84**:101–129.
- de Vos G, Kravvariti E, Collins J, Tavdy A, Nazari R, Hudes G et al. Increased allergic sensitization to mugwort in chronic urticaria. *Dermatology* 2012;**225**:141–146.
- Acevedo N, Vergara C, Mercado D, Jimenez S, Caraballo L. The A-444C polymorphism of leukotriene C4 synthase gene is associated with IgE antibodies to *Dermatophagoides pteronyssinus* in a Colombian population. *J Allergy Clin Immunol* 2007;**119**:505–507.
- Lamoureux J, Stankova J, Rola-Pleszczynski M. Leukotriene D4 enhances immunoglobulin production in CD40-activated human B lymphocytes. *J Allergy Clin Immunol* 2006;**117**:924–930.
- Kim DC, Hsu FI, Barrett NA, Friend DS, Grenningloh R, Ho IC et al. Cysteinyl leukotrienes regulate Th2 cell-dependent pulmonary inflammation. *J Immunol* 2006;**176**:4440–4448.
- Campo P, Ayuso P, Salas M, Plaza MC, Cornejo-García JA, Doña I et al. Mediator release after nasal aspirin provocation supports different phenotypes in subjects with hypersensitivity reactions to NSAIDs. *Allergy* 2013;**68**:1001–1007.