

ORIGINAL ARTICLE

Aspirin-exacerbated cutaneous disease (AECD) is a distinct subphenotype of chronic spontaneous urticaria

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Abstract

Background A subset of patients with chronic spontaneous urticaria (CSU) experience disease exacerbations after receiving non-steroidal anti-inflammatory drugs (NSAIDs). This condition has been designated as Aspirin-Exacerbated Cutaneous Disease (AECD).

Objectives The purpose of this study was twofold: (i) Investigate the demographic and clinical features of patients affected by AECD; (ii) To compare patients with AECD and NSAID-tolerant CSU patients for those characteristics.

Methods Patients with AECD and a group of unselected CSU patients tolerant to NSAIDs were studied. Demographic and clinical data were obtained by direct questioning and physical examination. Laboratory investigations and allergen skin prick tests were performed only in selected patients, as guided by the medical history.

Results Of 423 CSU patients admitted in the clinics, 52 (12.2%) had AECD. Compared with NSAID-tolerant CSU patients, AECD patients had significantly longer disease duration (57.7 ± 118.4 vs. 24.4 ± 36.6 months, $P < 0.05$), higher prevalence of angio-oedema (72.7 vs. 30.9%, $P < 0.05$) and atopy (83.8% vs. 58.4%, $P < 0.05$) and more frequent involvement of the face and upper respiratory tract (54.5% vs. 29.6%, $P < 0.05$).

Conclusions AECD is a distinct phenotype that should be considered for inclusion as a separate subtype of chronic spontaneous urticaria.

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Conflicts of interest

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Introduction

The International Guidelines for the definition, classification and diagnosis of urticaria recommend to distinguish two subgroups of chronic urticaria: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). CSU includes subtypes with a known cause (e.g. autoreactivity) and those without, whereas inducible urticarias encompass the physical urticarias (symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria and vibratory angio-oedema) as well as cholinergic, contact and aquagenic urticaria.¹

It was noticed more than 40 years ago that a substantial proportion of CSU patients experience disease exacerbations when they receive aspirin (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclooxygenase-1 isoenzyme of arachidonic acid metabolic pathway.² Analogous to

aspirin-exacerbated respiratory disease described by Stevenson *et al.*³ which is characterized by chronic rhinosinusitis, nasal polyposis, asthma and acute episodes of bronchospasm triggered by ASA and NSAIDs, we proposed that CSU aggravated by NSAIDs should be designated as aspirin-exacerbated cutaneous disease (AECD).^{4,5} This nomenclature has also been used by other authors in a book published recently.⁶

AECD is held to be a common condition, and NSAID-triggered exacerbations of CSU can be difficult to treat and result in substantial disability and quality of life impairment. As of now, the prevalence and clinical features of AECD remain ill characterized. The present investigation was performed to: (i) study the characteristics of patients with AECD and to (ii) compare the demographic and clinical features of AECD patients with those of CSU patients tolerant to COX-1 inhibitors.

Materials and methods

Unselected CSU patients attending the allergy outpatient clinic between 1 January 2011 and 31 December 2013 were studied. CSU was defined according to current International Guidelines as the appearance of weals and/or angio-oedema (AE) reoccurring for longer than 6 weeks.¹ AECD is defined as the appearance of ASA/NSAIDs-triggered weals or AE in patients affected by CSU.

AECD was confirmed by means of single-blind oral challenges with aspirin as previously described.^{7,8,9} For comparison, 371 unselected NSAID-tolerant CSU patients were included. Data on age, sex, duration of the disease, body distribution of the weals and AE, previous or present history of other medical conditions and NSAIDs inducing the aggravation of CSU were obtained by direct questioning and physical examination.

Laboratory investigations included complete blood cell count and differential. Erythrocyte sedimentation rate, C-reactive protein, total serum IgE, antinuclear and anti-thyroid autoantibodies, stool and urine analysis, complement C3 and C4, rheumatoid factor and serology for *Helicobacter pylori*. Skin prick tests with inhalant and food allergens were done with extracts from ALK-Abelló (Madrid, Spain). Both, laboratory tests and prick tests, were guided by the medical history and physical examination of patients, as recommended in the current Guidelines.¹ Informed consent was obtained from all patients included in this study, and the protocol was approved by the Ethics Committee of Clínica El Avila.

Statistical analysis: Comparison of categorical variables between groups was performed by Chi-squared test. Continuous variables are expressed as mean $\pm$ SD and were compared by Student's *t*-test. A value of $P < 0.05$ was considered significant.

Results

Demographic and clinical data

A total of 423 CSU patients were investigated for AECD. Fifty-two (12.2%) had a history and challenge-proven worsening of CSU symptoms when exposed to NSAIDs. Table 1 presents a summary of the demographic data of AECD patients and 371 unselected NSAID-tolerant patients with CSU. No differences in age or gender between the two groups were present. However, the duration of urticaria was significantly longer in patients with AECD ($P < 0.05$).

Figure 1 depicts the drugs involved in urticarial exacerbations in patients with AECD, and Table 2 shows the body distribution of weals and AE in AECD and NSAID-tolerant CSU patients. The most common NSAIDs implicated in the exacerbation of CSU were ibuprofen, diclofenac, aspirin and ketoprofen. Patients with AECD showed markedly increased rates and frequencies of angio-oedema and involvement of the head (mainly facial and upper respiratory tract AE) than NSAID-tolerant CSU patients, whereas generalized urticaria was more prevalent in non-AECD CSU patients ($P < 0.05$).

Table 1 Demographic and clinical data

	NSAID-tolerant CSU (n = 371)		AECD (n = 52)		P value
Age (years)	38.6 $\pm$ 17.1 (range 2–84)		42.4 $\pm$ 17.6 (range 11–84)		n.s.*
	n	%	n	%	–
Female	256	69.0	38	73.0	–
Male	115	30.9	14	26.9	n.s.#
Disease duration (months)	24.4 $\pm$ 35.6 (range 2–360)		57.7 $\pm$ 118.4 (range 2–540)		<0.05*

*Student's *t*-test.

#Chi-squared test.

n.s., not significant.

Data for age and disease duration are shown as means $\pm$ standard deviation of the mean.

A history of hypothyroidism, allergic rhinitis and asthma was present in 12% and 17.3%, 10% and 9.6%, and 8% and 7.6% of patients with NSAID-tolerant CSU and AECD patients respectively. Other comorbidities, including hypertension, chronic rhinosinusitis, diabetes, migraine, nephrolithiasis and atopic dermatitis were present in less than 8% in both groups (data not shown).

Laboratory investigations and skin tests

Two hundred and thirty-three NSAID-tolerant patients and 24 AECD patients were submitted to complementary tests (Table 3). Increased total immunoglobulin E, antithyroid antibodies and antinuclear antibodies, were the most frequent abnormalities found in the CSU group, but rates were not statistically different from those found in AECD patients. Erythrocyte sedimentation rate was significantly increased in patients with AECD ($P < 0.05$).

Allergen skin tests were positive in 83.8% of AECD patients and in 58.4% of NSAID-tolerant CSU patients ($P < 0.05$) (Table 4), and this difference was mainly due to a higher frequency of sensitization to domestic mites *Dermatophagoides pteronyssinus* and *Blomia tropicalis* ($P < 0.05$).

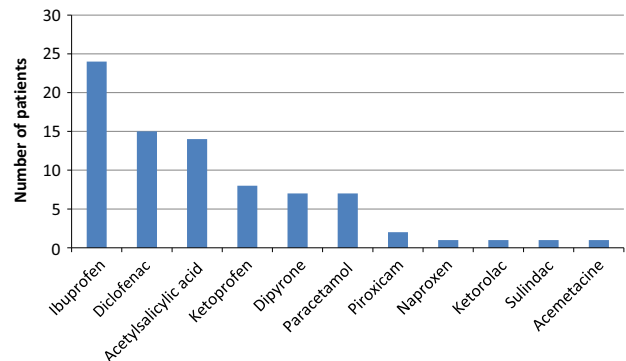


Figure 1 NSAIDs responsible for disease exacerbation in AECD patients based on data from patient's interrogation.

Table 2 Body distribution of weals and angio-oedema

Body distribution	Urticaria		P value*	Angio-oedema		P value*
	NSAID-tolerant CSU n (%)	AECD n (%)		NSAID-tolerant CSU n (%)	AECD n (%)	
Head	36 (9.7)	1 (2.2)	n.s.	78 (21.0)	22 (50.0)	<0.05
Neck	19 (5.1)	3 (6.8)	n.s.	0 (0)	0 (0)	n.s.
Trunk	69 (18.5)	12 (27.2)	n.s.	0 (0)	0 (0)	n.s.
Upper limbs	91 (24.5)	13 (29.5)	n.s.	6 (1.6)	0 (0)	n.s.
Lower limbs	83 (22.3)	14 (31.8)	n.s.	1 (0.2)	0 (0)	n.s.
Generalized	93 (25.0)	10 (22.7)	n.s.	0 (0)	0 (0)	n.s.
Weals alone	256 (69.0)	13 (29.5)	<0.05	–	–	–
Angio-oedema alone	38 (10.2)	11 (25.0)	<0.05	–	–	–
Weals + angio-oedema	77 (20.7)	21 (47.7)	<0.05	–	–	–
Total angio-oedema	115 (30.9)	32 (72.7)	<0.05	–	–	–

*Chi-squared test.

n.s., not significant.

Table 3 Abnormal laboratory tests in patients with NSAID-tolerant CSU and AECD

Test	NSAID-tolerant CSU (n = 233)		AECD (n = 24)		P value*
	N	%	n	%	
Increased IgE	17	7.2	3	12.3	n.s.
Blood eosinophilia	16	6.8	2	8.3	n.s.
Increased ESR	4	1.7	2	8.3	<0.05
Antithyroid antibodies	14	6.0	1	4.1	n.s.
Antinuclear antibodies	4	1.7	1	4.1	n.s.
Increased CRP	2	0.8	1	4.1	n.s.
IgG anti- <i>H. pylori</i>	2	0.8	1	4.1	n.s.
Other	B. hominis in stools (7), increased TSH (5), increased aminotransferases (5), hyperuricemia (2), microscopic haematuria (1), increased lactic dehydrogenase (1), increased alkaline phosphatase (1) positive syphilis serology (1), decreased TSH (1), A.lumbricoides in stools (1), proteinuria (1), bacteriuria (1), hypercholesterolemia (1)		E. nana in stools (1) G. lamblia in stools (1)		

*Chi-squared test.

Discussion

This investigation assessed the demographic and clinical features of patients with AECD. The prevalence of AECD in patients with CSU in this study was 12.5%, a lower proportion than the 21–30% figure reported in the literature.¹⁰ However, it is important to notice that there are no published data specifically looking at the frequency of AECD in groups of patients with CSU large enough to draw a reasonable comparison with our present results.

When comparing the demographic data from AECD patients and NSAID-tolerant CSU patients, no significant differences in regard to age or gender were observed. Nevertheless, patients with AECD had a significantly longer duration of the disease, which may suggest a different pathogenesis and/or a more severe disease.

The body distribution of the urticarial skin lesions was different between the two groups: patients with AECD had a more

frequent involvement of the head, mainly due to face (mostly eyelid, lip and upper respiratory tract) angio-oedema. The frequent occurrence of upper respiratory tract and laryngeal angio-oedema would also confer AECD a higher risk and severity due to possible asphyxia, a potentially life-threatening condition.

Regarding the NSAIDs involved in the exacerbation of CSU in AECD patients, most of them are potent inhibitors of COX-1 such as aspirin, ibuprofen, diclofenac and ketoprofen (Fig. 1). More rarely, some patients had symptoms triggered by paracetamol, a weak COX-1 inhibitor. These patients belong to the 'high risk' group of reactors to NSAIDs previously proposed by our group.¹¹ In general, responsible NSAIDs vary between geographical regions depending on the availability of the drugs and local physician prescription patterns. For analgesic and anti-inflammatory therapy in NSAID-intolerant patients we usually recommend weak COX-1 inhibitors such as preferential

Table 4 Results of skin prick tests with allergenic extracts

	NSAID-tolerant CSU (n = 231)		AECD (n = 31)		P value*
	N	%	n	%	
Positive	135	58.4	26	83.8	<0.05
<i>D. pteronyssinus</i>	110	47.6	22	70.9	<0.05
<i>B. tropicalis</i>	105	45.4	22	70.9	<0.05
<i>D. farinae</i>	52	22.5	7	22.5	n.s.
Cockroach	36	15.5	5	16.1	n.s.
Foods	35	15.1	5	16.1	n.s.
Dog	34	14.7	7	22.5	n.s.
Cat	25	10.8	2	6.4	n.s.
Moulds	13	5.6	3	9.6	n.s.
Feathers	7	3.0	2	6.4	n.s.
<i>Ragweed</i>	5	2.1	1	3.2	n.s.
<i>Chenopodium</i>	4	1.7	1	3.2	n.s.
Other	Grass mix (8), <i>Plantago lanceolata</i> (1), <i>Cypress</i> (1)				

*Chi-squared test.

n.s., not significant.

(meloxicam and nimesulide), or selective COX-2 inhibitors (etoricoxib, celecoxib).^{7,12}

In this study, we have observed a higher frequency of atopy in patients with AECD when compared with NSAID-tolerant CSU patients (Table 4). We have reported previously an association of NSAID sensitivity and atopic trait which in the tropics is more often related to sensitization to mites,¹³ and increased levels of total and mite-specific IgE in patients with aspirin-induced urticaria and angio-oedema.¹⁴ The possible mechanisms explaining this relationship have been discussed in a recent article.¹⁵ Another report has shown that AECD patients have higher rates of asthma, nasal polyps and dermatographism as well as a higher risk to develop asthma and rhinitis as compared to NSAID-tolerant CSU patients.¹⁶

Additional information supporting the distinct features of AECD may reside in the description of various genetic polymorphisms associated with NSAID hypersensitivity.^{16–18}

In conclusion, we have observed some clinical features in patients with AECD that distinguish them from NSAID-tolerant CSU individuals, such as a longer disease duration, increased prevalence of angio-oedema and atopic trait. We propose that AECD should be included as a distinct phenotype of CSU in future revisions of the Guidelines for Diagnosis and Management of Urticaria and Angioedema. In addition to this, these findings suggest that all CSU patients should be explored for AECD and that AECD patients should be assessed for angio-oedema and comorbid allergies and treated appropriately.

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