

Report

Chronic idiopathic angioedema: a single center experience

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Abstract

Objective Chronic idiopathic angioedema (CIA) is defined as three or more episodes of angioedema in a period of > 6 months without a clear etiology. In the study, we tried to explore clinical and laboratory characteristics of patients with CIA unaccompanied by urticaria.

Methods We retrospectively reviewed clinical and laboratory characteristics of 1238 patients with chronic urticaria and/or angioedema referred to our allergy clinic.

Results Eight hundred and forty-one (67.9%) subjects had chronic urticaria without angioedema (CU Group), 323 (26.1%) had both urticaria and angioedema (CU + CA group), and 74 (5.9%) had chronic angioedema without urticaria (CA). In 29 (39.2%) cases of CA, no etiologic factor of angioedema was discovered, thus the patients were defined as having chronic idiopathic angioedema (CIA Group). Twenty-two (75.8%) subjects had antihistamine-responsive CIA and seven (24.1%) had antihistamine-unresponsive CIA. There were no statistically significant differences in clinical (except of urticarial eruptions) and laboratory characteristics between CU, CA + CU, and CIA groups. Antihistamine responsive and antihistamine-unresponsive CIA groups had no distinguishable clinical or laboratory features.

Conclusions We suppose that CIA, at least its antihistamine-responsive form, represents a rare form of chronic spontaneous urticaria. The reasons why in CIA there are no other clinical signs of mast cell/basophil activation, such as pruritus, urticarial, and dermatographism, are largely unknown and have to be elucidated in future studies.

Introduction

Angioedema is defined as a self-limited, localized swelling, which occurs in approximately 15% of the general population.¹ The most frequent syndrome of chronic angioedema (CA) is chronic idiopathic angioedema (CIA), which occurs in 38% of patients with CA, even after a thorough clinical and laboratory evaluation.² Chronic spontaneous urticaria (CSU) is associated with angioedema in about 30% of cases.¹ However, in 10% cases, angioedema occurs alone.¹ There is no consensus in the definition of CIA. By some groups, episodes of angioedema persisting six weeks in duration are considered as chronic,² while others defined CIA as three or more episodes of angioedema in a period of > 6 months without a clear etiology.³

Chronic idiopathic angioedema appears to be antihistamine responsive in most cases, but in 14% of patients, it has antihistamine-unresponsive features.⁴ Antihistamine-responsive patients have probably mast-cell-mediated angioedema, and non-responders have probably bradykinin-mediated angioedema. Bradykinin is known to play a

major role in the pathophysiology of antihistamine unresponsive recurrent angioedema caused by hereditary or acquired C1-inhibitor deficiency or by treatment with angiotensin-converting enzyme inhibitors.^{5,6}

Chronic idiopathic angioedema, not associated with urticaria, is a diagnosis of exclusion after a patient's thorough evaluation, but its real epidemiology and natural history are largely unknown.⁷ In this study, we tried to explore clinical and laboratory characteristics of patients with CIA unaccompanied by urticaria.

Methods

The study was performed at our Allergy and Clinical Immunology referral center in the Lakhish district of southern Israel. The study protocol was approved by the local Institutional Ethical Review Committee. We retrospectively reviewed the electronic medical records of all outpatient allergy consultations due to a diagnosis of CSU and CA from January 1, 2002, to March 31, 2012. CSU was defined as weals and/or angioedema arising spontaneously, when the disease lasts > 6 weeks. CA was defined as three or more episodes of

angioedema without urticaria in a period of > 6 months without a clear etiology.³

In the study, we included all subjects ≥ 18 years. As part of the standard practice in our allergy clinic, all subjects had been informed about any risks involved with testing, and written informed consent for allergologic work-up (skin prick test, autologous serum skin test [ASST]) had been obtained. Written informed consent was given by control group participants.

Patients with other underlying etiologies of chronic urticaria (urticarial vasculitis, physical urticaria, thyroid diseases, systemic lupus erythematosus, food allergy, malignancy) and angioedema (hereditary angioedema, acquired C1-inhibitor deficiency, angiotensin-converting enzyme inhibitor-related angioedema, food or drug allergy induced angioedema, other causes of peripheral or generalized edema) were excluded.

The following data were collected from the computerized database:

- 1 Demographic records, chest and sinus x-ray studies,
- 2 Results of ASST, if done,
- 3 Laboratory work-up results: liver and renal function tests, complete blood count, erythrocyte sedimentation rate, high-sensitivity C-reactive protein (hs-CRP), thyroid function tests, antinuclear, antithyroglobulin, and antiperoxidase antibodies, C3, C4, serum protein electrophoresis, and IgE.

Clinical and laboratory evaluation and classification of chronic urticaria and angioedema were performed according to the EAACI/GA(2)LEN/EDF/WAO guidelines,⁸ and the patients were treated according to the current guidelines on the management of urticaria.⁹ Fexofenadine hydrochloride (Telfast; sanofi-aventis, Netanya, Israel) 180 mg b.i.d. was used as the drug of choice in the treatment of patients with CIA. The patients were re-examined every 14 days to assess antihistamine treatment efficacy.

Laboratory tests were performed before beginning treatment with antihistamine medications, on the next day following the first allergy consultation.

Autologous serum skin test

ASST was performed with 50 μ l of the patient's undiluted serum after allowing blood to clot at room temperature for 30 minutes and sample blood centrifugation at 500 *g* for 10 minutes, which was then injected intradermally into the volar aspect of the forearm together with simultaneously injected controls, including saline and 10 μ g/ml histamine. The mean diameters of the weals were measured at 30 minutes. A minimum difference of 1.5 mm in mean perpendicular weal diameter between the autologous serum (AS)-induced response and the saline-induced response was used to define ASST positivity.

Complement tests

Serum was used for analyses of autoantibodies and for the functional complement analyses. C3 and C4 component levels were measured by the ABICAP assay (Biognosis, Jülich,

Germany). The normal standardized values for each component were 80–180 mg/dl for C3 and 10–40 mg/dl for C4. C1 esterase inhibitor antigen level was measured by single radial immunodiffusion (NOR-Partigen; Behringwerke A/G, Marburg, Germany) and performed according to the manufacturer's instructions (normal range 0.18–0.54 g/l). C1-inhibitor function was assayed by functional enzyme-linked immunosorbent assay (Quidel, San Diego, CA, USA; normal range > 84%).

Other laboratory tests

Thyroxine and thyroid-stimulating hormone levels were measured by a solid phase competitive analogue sequential chemiluminescent immunoassay (Immulite 2000; DPC, Los Angeles, CA, USA).

Blood levels of hs-CRP were measured by immunonephelometry using BN systems (Dade Behring, Marburg, Germany), and the reference interval for hs-CRP was 1–3 mg/l.

Antinuclear antibodies were determined by a commercially available indirect immunofluorescence test kit (ANAFastTM kits; Diasarin, Stillwater, MN, USA) using HEP-2 cells as substrate, and titers above 1/40 were considered positive.

Statistical analysis

Data with normal distribution were presented as mean $\pm$ standard deviation (mean $\pm$ SD). Categorical data were compared using the chi-squared and Fisher's exact tests (two tailed). One-way analysis of variance (ANOVA) and Bonferroni *post hoc* examination were carried out for comparisons between the four groups (CIA, CU + CA, CU, and control) to evaluate whether statistically significant differences exist among the groups. Level of significance $P < 0.05$ and with Bonferroni adjustment was $P < 0.0125$. Antihistamine-responsive and antihistamine-unresponsive subgroups were compared using Fisher's exact test (two tailed). Level of significance was $P < 0.05$.

Statistical analysis was performed using Statistical Package for the Social Sciences version 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics of the study groups are presented in Table 1. During the study period, 1238 patients with chronic urticaria and/or angioedema lasting > 6 weeks were referred to our allergy clinic. Eight hundred and forty-one (67.9%) patients had chronic urticaria without angioedema (CU group), 323 (25.8%) had both urticaria and angioedema (CU + CA), and 74 (5.9%) had angioedema alone (CA). Among 74 patients with CA, recurrences of angioedema were definitely related to exogenous stimuli in 45 (60.8%) cases, while no case of CA triggered by food, infection, or physical stimuli was

identified (Table 2). In 29 (39.2%) cases of CA, no etiologic factor was discovered, thus the patients were defined as having CIA. The control group consisted of 44 sex- and age-matched healthy individuals recruited from the hospital and the primary care center staff. There were no statistically significant differences in most clinical characteristics between the CU, CU + CA, and CIA groups. In the CIA group, more patients with angioedema affecting the oropharynx (five, 17.3%) and genital regions (four, 13.4%) were observed compared to the CU + CA group (four, 1.2%, $P < 0.001$; seven, 2.2%, $P = 0.01$, respectively).

From the laboratory characteristics, there was a statistically significant difference in CRP levels between the CU + CA (2.62 ± 1.39 mg/l) and CU (2.87 ± 1.42 ; $P = 0.007$) groups but not between other pairs of the study groups. Basophils were lower in the CIA (0.04 ± 0.07 cell/mm³), CU + CA (0.03 ± 0.09 cell/mm³), and CU (0.04 ± 0.05 cell/mm³) groups, than in

the control group (0.19 ± 0.14 cell/mm³; $P < 0.001$); but no statistically significant difference in basophils was observed between the CIA, CU + CA, and CU groups (after Bonferroni correction) (Table 1).

Under antihistamine treatment, 22 (75.8%) CIA subjects were without angioedema attacks at week 8. These patients were defined as having antihistamine-responsive CA. Seven (24.2%) patients had at least one attack of angioedema during the 8-week antihistamine treatment. These subjects were considered as having antihistamine-unresponsive CIA and were treated with daily tranexamic acid (Hexakapron 500 mg; Teva Pharmaceutical, Petach Tikva, Israel) 1 g t.i.d. With tranexamic acid continuous therapy, angioedema attacks disappeared completely in five (71.4%) patients, and in two (28.6%) their frequency and severity were significantly reduced.

All 29 patients in the CIA group reported a history of recurrent angioedema involving different sites (mostly

Table 1 Demographic and laboratory data of study groups

Characteristics	CIA n = 29	CU + CA n = 323	CU n = 841	Controls n = 44	P value
Sex; female	18 (62.1%)	219 (67.8%)	546 (64.9%)	28 (63.6%)	NS
Age (years)	39.7 ± 15.6	42.5 ± 15.8	40.9 ± 14.3	40.1 ± 14.5	0.34
Age at disease onset (years)	36.5 ± 15.3	39.1 ± 16.2	37.4 ± 14.9	—	0.31
Disease duration; (months)***	39.2 ± 27.7	35.1 ± 33.4	38.3 ± 35.6	—	0.36
BMI, kg/m ²	27.4 ± 4.2	27.2 ± 3.9	27.1 ± 3.8	27.1 ± 4.6	0.96
AE affecting the face	26 (83.4%)	259 (80.2%)	—	—	0.32
AE affecting the hands and/or feet	19 (63.6%)	195 (60.4%)	—	—	0.69
AE affecting the oropharynx	5 (13.4%)	4 (1.2%)	—	—	< 0.001
AE affecting the genitalia	4 (13.4%)	7 (2.2%)	—	—	0.01
Life-threatening AE attacks	1 (3.5%)	0	—	—	0.08
Total IgE (1–87) U/ml	117.2 ± 40.9	112.3 ± 51.5	115.7 ± 53.2	112.6 ± 54.9	0.69
ESR (mm/h)	12.7 ± 10.5	14.9 ± 12.7	13.5 ± 12.1	14.1 ± 11.3	0.59
ESR (> 20 for females, > 15 for males) (mm/h), n (%)	3 (10.3%)	37 (11.4%)	82 (9.8%)	5 (11.3%)	NS
WBC (cell/mm ³)	7.8 ± 3.9	7.7 ± 4.1	7.4 ± 4.3	7.3 ± 3.2	0.70
Lymphocytes (cell/mm ³)	2.3 ± 1.1	2.6 ± 1.4	2.4 ± 1.2	2.5 ± 1.3	0.11
Eosinophils (0–0.54) (cells × 10 ⁹ /l)	0.42 ± 0.19	0.38 ± 0.25	0.43 ± 0.21	0.39 ± 0.27	0.26
Eosinophils > 0.54 (cells × 10 ⁹ /l) n (%)	6 (20.7%)	47 (14.6%)	107 (12.7%)	5 (11.3%)	NS
Basophils (0–0.18) (cells × 10 ⁹ /l)	0.04 ± 0.07	0.03 ± 0.09*	0.04 ± 0.05**	0.19 ± 0.14	< 0.001
Platelets (cells × 10 ⁹ /l)	269 ± 135	274 ± 125	271 ± 143	267 ± 141	0.98
C3 (g/L)	1.23 ± 0.22	1.29 ± 0.34	1.31 ± 0.28	1.23 ± 0.31	0.15
C4 (g/L)	0.33 ± 0.15	0.35 ± 0.19	0.34 ± 0.17	0.32 ± 0.16	0.65
TSH (0.35–4.94 mIU/l)	2.51 ± 0.82	2.45 ± 0.87	2.54 ± 0.79	2.41 ± 0.63	0.31
TSH > 4.94 mIU/l, n (%)	1 (3.4%)	17 (5.2%)	36 (4.3%)	1 (2.3%)	NS
TSH < 0.35 mIU/l, n (%)	0	3 (0.9%)	7 (0.8%)	0	NS
ANA (positive > 1/80)	4 (13.7%)	29 (6.8%)	74 (7.8%)	2 (4.5%)	NS
C-reactive protein (mg/l)	2.84 ± 1.45	2.62 ± 1.39	2.87 ± 1.42***	2.75 ± 1.58	0.07

ANA, antinuclear antibodies; CU + CA, chronic idiopathic urticaria with angioedema; CIA, chronic idiopathic angioedema; CU, chronic idiopathic urticaria without angioedema; ESR, erythrocyte sedimentation rate; NS, P value statistically non-significant between any pairs of the groups; TSH, thyroid-stimulating hormone.

* $P < 0.001$ between CU + CA and control groups.

** $P < 0.001$ between CU and control groups.

*** $P = 0.007$ between CU + CA and CU groups.

Significant P after Bonferroni correction ($P < 0.0125$; $\alpha = 0.05/4$ tests = 0.0125).

Table 2 Patients with chronic angioedema without urticaria ($n = 74$)

Classification	Patients (n/%)	Etiologic factors
ACE inhibitor related	28 (37.8)	ACE inhibitors
Other drug related*	8 (10.8)	NSAID – 3 (4.1%) Aspirin – 2 (2.7%) Bupropion – 1 (1.4%) Selective serotonin reuptake inhibitor – 1
Autoimmune disease**	7 (9.5)	Autoimmune thyroiditis – 3 (4.1%) Systemic sclerosis – 3 (4.1%) Raynaud's phenomenon – 2 (2.7%)
C1-inhibitor deficiency		
Hereditary	2 (2.7)	
Acquired	0	
CIA	29 (39.2)	

ACE, angiotensin converting enzyme; CIA, chronic idiopathic angioedema; NSAID, nonsteroidal anti-inflammatory drugs.

* $P < 0.05$.

** $P < 0.001$.

affecting the face, hands, and feet). There were no severe or life-threatening angioedema attacks in both antihistamine-responsive and antihistamine-unresponsive CIA groups. There were no statistically significant differences of clinical and laboratory characteristics between the antihistamine-responsive and antihistamine-unresponsive CIA groups (Table 3).

Discussion

In the study, we explored a large cohort of patients referred to the allergology referral center due to chronic urticaria and/or angioedema and recognized that 2.4% of patients were characterized by a history of recurrent angioedema which was not accompanied by urticaria and was not triggered by identified external agents, including foods, drugs, Hymenoptera venom, or physical stimuli. None of them had a family history of angioedema or were taking angiotensin-converting enzyme inhibitors. Serum levels of the complement fractions C3 and C4, antigenic C1-inhibitor levels and functional C1-inhibitor levels, as well as serum protein electrophoresis were normal in all cases. Therefore, these patients were defined as suffering from CIA. Although CIA is felt to be the most common cause of CA, its true epidemiology is not known. It was previously recognized that in about 10% cases of CSU, angioedema occurs alone without accompanying urticaria.^{1,8} This number is much higher than the 2.4% found in our study, and this discrepancy might be explained by the fact that the previous estimation was drawn from rather small cohorts having CSU.⁸ In a previ-

ous study of 776 patients with recurrent angioedema without urticaria, 38% of cases were defined as CIA,⁴ and we diagnosed CIA in 39.2% of patients with CA.

Nowadays, the natural course of CIA is largely unknown, although it is accepted that many patients with CSU will suffer for more than one year or much longer.¹⁰ The mean duration of the disease in our study was similar in the CIA, CU, and CU + CA groups. Moreover, there was definitely no difference in the clinical (except the presence of urticaria) and laboratory characteristics between the CIA, CU, and CU + CA groups. Therefore, our observation is in agreement with the accepted assumption that CIA possibly represents a clinical variant of CSU. Currently, in CIA, a trial of non-sedating antihistamines, administered twice daily, is suggested as an initial intervention.⁴ As in the previous study,⁴ we also observed a significant improvement or resolution of the angioedema with this intervention in most of our patients, although other experts describe less success in preventing angioedema recurrence even with higher doses of antihistamines and no response in up to 30% of patients with CIA.^{6,11} Responsiveness to antihistamines may suggest a possible role of mast-cell- or basophil-mediated processes in the pathophysiology of antihistamine-responsive CIA. Mast-cell-mediated angioedema is pathologically similar to urticaria, although it takes place in the deeper levels of the dermis and subcutaneous tissues.⁶ The reason why in CIA there are no other clinical signs of mast cell/basophil activation, such as pruritus, urticarial, and dermatographism, is largely unknown and will have to be elucidated in future studies.

Another interesting observation of the study is the lack of difference in clinical or laboratory features between patients with antihistamine-responsive and antihistamine-unresponsive CIA. We have observed an impressive and sustained clinical effect of tranexamic acid in most cases of antihistamine-unresponsive CIA that is in agreement with previous observations.^{4,12–14} The pathophysiology of antihistamine-unresponsive CIA is mostly speculative, and several biological mediators acting as triggers or enhancers of vascular permeability have been implicated.^{15,16} Recently, investigational therapies (dapson, icatibant [bradykinin B2 receptor antagonist], and rituximab [B-cell depleting anti-CD20 monoclonal antibody]) have been reported in severe and refractory cases.^{17–19}

An additional finding of our study is that some patients with antihistamine-responsive and antihistamine-unresponsive CIA react to intradermal injection of AS. This is a discrepancy with a previous study by Tedeschi *et al.*,²⁰ which reported that patients with CIA have a negative ASST and do not show significant circulating histamine-releasing activity, unlike patients with CU and CU + CA, who often show autoreactivity. This finding

Table 3 Clinical and laboratory characteristics of patients with antihistamine-responsive CIA and antihistamine-unresponsive CIA

Characteristics	Antihistamine-responsive CIA <i>n</i> = 22 (75.9%)	Antihistamine-unresponsive CIA <i>n</i> = 7 (24.1%)	<i>P</i> value
Sex; female <i>n</i> (%)	15 (68.2%)	3 (42.9%)	0.37
Age (years)	41.2 ± 14.9	38.1 ± 18.5	0.65
Age at disease onset (years)	37.6 ± 13.2	35.7 ± 17.1	0.76
Duration of angioedema attacks (h)	36.4 ± 31.7	42.1 ± 34.2	0.69
Number of angioedema attacks ^a	4.2 ± 0.9	4.3 ± 1.1	0.81
Number of angioedema attacks ^b	0	1.8 ± 0.7	< 0.001
AE affecting the face	19 (83.4%)	7 (100%)	0.56
AE affecting the hands and/or feet	14 (63.6%)	5 (71.4%)	0.68
AE affecting the oropharynx	3 (13.4%)	2 (28.6%)	0.57
AE affecting the genitalia	3 (13.4%)	1 (14.2%)	1
Recurrent abdominal pain	0	1 (14.2%)	0.24
Life-threatening attacks	0	0	1
Pruritus between/or during AE	0	0	1
Dermatographism	0	0	1
Positive ASST, <i>n</i> (%)	7 (31.8%)	2 (28.5%)	1
Total IgE (1–87 U/ml)	121.8 ± 44.1	104.4 ± 33.8	0.35
Total IgE > 87 U/ml <i>n</i> (%)	10 (45.5%)	3 (42.9%)	1
C3 (g/l)	1.21 ± 0.24	1.25 ± 0.19	0.69
C4 (g/l)	0.35 ± 0.13	0.31 ± 0.11	0.47
C1 inhibitor (g/l)	0.33 ± 0.21	0.37 ± 0.16	0.65
Functional C1-inhibitor (%)	114 ± 15	109 ± 11	0.42
Eosinophils (0–540) cell/mm ³	0.39 ± 0.24	0.35 ± 0.26	0.71
Eosinophils > 540 cell/mm ³	5 (22.7%)	1 (14.3%)	1
ESR (mm/h)	15.2 ± 9.7	14.4 ± 13.1	0.86
ESR (> 20 for females, > 15 for males) (mm/h), <i>n</i> (%)	4 (18.2%)	1 (14.3%)	1
ANA (positive > 1/80), <i>n</i> (%)	3 (13.6%)	1 (14.3%)	1
TSH (0.35–4.94 mIU/l)	2.63 ± 0.86	2.49 ± 0.78	0.71
TSH > 4.94 mIU/l, <i>n</i> (%)	2 (9.1%)	1 (14.3%)	1
TSH < 0.35 mIU/l, <i>n</i> (%)	0	0	1

AE, angioedema; ANA, antinuclear antibodies; ASST, autologous serum skin test; CIA, chronic idiopathic angioedema; ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone.

^aNumber of angioedema attacks during 6 months before the antihistamine treatment initiation.

^bNumber of angioedema attacks during 2 months under treatment of fexofenadine 180 mg b.i.d.

may be explained, at least in part, by the small number of patients with CIA in our cohort.

Several recent studies observed a higher frequency of positive ASST in CU + CA patients than in patients with CU.^{21,22} Intradermally injected factors in AS are acting either indirectly through the release of mediators from cutaneous mast cells or other cells, or directly on the microvasculature of skin.²³ Autoreactivity may be an indication of mast cell activating autoantibodies in patients with ASST-positive CIA.²⁴ In a recent experimental study, mast cells were found to be critically involved in serum-mediated vascular leakage in CSU through an IgE- and IgG-independent mechanism,²⁵ and these cells are present in increased numbers in the skin of patients with CSU.²⁶ Histamine, when released, acting through its H₁ receptor, leads to parasympathetic nerve stimulation and increased vascular permeability,²⁷ which in turn results in the formation of angioedema.²⁸

The recently proposed gold standard for autoimmune CSU diagnosis should be a combination of a positive bioassay (basophil histamine release assays or basophil activation marker expression), positive autoreactivity (by means of a positive ASST), and a positive immunoassay (for specific IgG autoantibodies against FcεRIα and/or anti-IgE).²⁹ If we consider CIA as a special subtype of CSU, an additional bioassay and immunoassays have to be performed, which would allow to confidently distinguish subjects with autoimmune mechanisms from those with other etiological patterns of CA.

We recently observed a lack of suppression of AS-mediated weal induction by high-dose antihistamines in some patients with CSU, which supports a role played by other biological factors, possibly present in serum of patients with CSU, and may be responsible for weal and flare reactions by increasing endothelial permeability and endothelial cell leakage.³⁰ The hypothesized biological factors

in AS may be related to bradykinin-forming cascade and the complement pathways.³¹

An additional interesting observation of the study is that affection of oropharyngeal and genital regions were more commonly seen in CIA than in patients with CU + CA. Oropharyngeal and genital angioedema in CIA may be induced both by histamine³² and/or by bradykinin.¹² We can only speculate that in CIA the contact pathway and bradykinin production are more activated than in CU + CA, which leads to increased vascular permeability and vasodilation in the body areas with relatively little supporting connective tissue, where edema develops easily.

The latest studies have also found that activation of the coagulation cascade resulting in thrombin production is associated with CSU.^{33–35} Moreover, several studies have shown that thrombin participates in mast cell degranulation by activating protein kinase receptors on the mast cell surface.³⁵ Thrombin and bradykinin initiate discrete endothelial solute permeability in cutis and mucosa.³⁶ Additionally, complement activation with C5a (anaphylotoxin) generation in the absence of C3 by thrombin takes the place in CSU.³⁷ Therefore, it has been proposed that CSU is a disease at the crossroads between autoimmunity and coagulation.³⁸ To evaluate thrombin activation in CIA, the autologous plasma skin test could be performed.³⁹ Regretfully, we did not perform the autologous plasma skin test in our patients, and this issue is to be investigated in future studies.

Chronic spontaneous urticaria is now considered as a mast cell- and basophil-dependent inflammatory disorder accompanied by low-grade systemic inflammation,⁴⁰ which is reflected by increased serum CRP.⁴¹ In our study, serum levels of CRP were significantly higher in CU + CA, than in patients with CU. This finding is in agreement with our previous study⁴² and other studies,^{43,44} which showed that CRP increases corresponded to the severity and activity of CSU. Furthermore, the study revealed lower basophils in the CIA, CU + CA, and CU groups, than in the control group. Basopenia in CSU is well recognized from previous studies.^{42,45–47} Circulating basophils may be recruited from blood into urticarial weals during disease activity, and basopenia was found associated with serum basophil histamine-releasing activity in patients with CSU.⁴⁶ Besides the basopenia, intrinsic defects of the anti-IgE cross-linking signaling pathway of basophils have been described in CSU.⁴⁸

In summary, our study provides an overview of CIA based on its clinical and laboratory features. We understand that the study has several limitations, mainly related to its retrospective nature with a possible recording bias and a small number of subjects. The lack of evidence about activation of the coagulation cascade resulting in

thrombin production in CIA is an additional limitation of our study. Bigger prospective, multicenter epidemiological studies are needed to better characterize CIA.

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