

# Clinical and functional differences among patients with idiopathic anaphylaxis

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## Summary

**Background:** There are no studies assessing whether patients with idiopathic anaphylaxis are a heterogeneous population

**Objective:** A study has been carried out to assess whether clinical and functional differences (mast cell releasability) exist between two sub-types of Idiopathic Anaphylaxis (Generalized Idiopathic Anaphylaxis -IA-G- and Idiopathic Anaphylaxis with Angioedema -IA-A-).

**Methods:** Patients were selected from the Idiopathic Anaphylaxis (IA) patient population of Hospital General de Albacete (Albacete, Spain) and this data were collected between 1990 and 1995. This series is composed of 81 patients. In the interest of seeing whether an IA classification is warranted between IA-G and IA-A, a logistic regression model was constructed in order to know if differences exist between IA-G and IA-A.

To evaluate mast cell releasability in different groups (IA-G, IA-A, atopic patients, urticaria and healthy subjects) we analysed the log<sub>10</sub> wheal area produced by four consecutive concentrations of codeine (from 90 to 3,3 mg/ml). In those patients with IA-G, the variable urticaria was controlled, but not in those with IA-A. A parallel line assay was used to study the differences arising among all groups. When the conditions of parallelism and linearity were not fulfilled, a Hotelling's T<sub>2</sub> test was performed.

**Results:** In the logistic regression equation total IgE, with an O.R. of 1.006 (95% C.I. 1.001-1.01) favoured the presence of IA-G; whereas the presence of urticaria did not favour the presence of IA-G, with an O.R. of 0.159 (95% C.I. 0.04 – 0.507).

IA-G and IA-A patients showed a higher cutaneous reaction to codeine than atopic patients (p=0.005 and p=0.001 respectively). However, IA-G patients had a lower reaction to codeine than those patients with urticaria (p=0.048). No differences were observed among patients with IA-A and patients with urticaria, as was the case between IA-A and IA-G patients with respect to cutaneous response to codeine.

**Conclusion:** Apparently, IA-G patients appear to be closely related to the presence of atopy, while IA-A patients are closely related to the presence of urticaria. Along with other unknown factors, an enhanced mast cell releasability may explain these episodes of Idiopathic Anaphylaxis among atopic patients.

**Key-words:** Idiopathic, anaphylaxis, angioedema, generalised, codeine, releasability, atopy, urticaria.

## Introduction

Patients exhibiting Idiopathic Anaphylaxis (IA) have been classified into two groups, Generalized Idiopathic Anaphylaxis (IA-G) and Idiopathic Anaphylaxis with

Angioedema (IA-A), depending upon whether the disorder is of a systemic nature or it only affects the upper respiratory airways [1,2]. The aforementioned division is based on the recurrence of the same clinical presentation of this disorder over time [3]. However,

the clinical and immunological differences between these sub-types have rarely been investigated.

On the other hand, several hypotheses have been proposed to explain the pathogenesis of IA. It has been speculated whether in IA patients there exists a spontaneous release of histamine and other mediators originated in mast cells or basophils due to an enhanced releaseability. This hypothesis has not been proved in several studies [4,5]. Nevertheless, it has not been tested using other designs, and in addition it has not been studied if releasability is different in IA-A and IA-G patients.

Our purpose is to establish whether there exist clinical and immunological differences between IA-G and IA-A patients, and also to explore mast cell releaseability in both sub-types.

## Patients, materials and methods:

### Study Design and Patients

In order to establish whether an IA classification (IA-A and IA-G) is warranted, we studied whether clinical, analytical and immunological variables were distributed in the same or in a different manner between both subgroups. Patients were selected from the IA patient population of Hospital General de Albacete (Albacete, Spain), and were 81. In a previous paper [6], we have reported on the clinical characteristics of the series (data related to episodes of anaphylaxis and the presence of atopic diseases and urticaria) which were obtained and recorded for all 81 patients in the series at the moment of their first visit.

In order to study whether mast cell releaseability in those patients with IA is enhanced, a cutaneous response to codeine was studied by means of skin prick test. This test has been described as a simple method to measure the capacity of mediators release from cutaneous mast cells [7]. The cutaneous response to codeine was carried out on a group of patients with IA-G (n=9) and IA-A (n=10), and in several control groups composed of healthy subjects (n=10), patients with atopy (n=18) and urticaria (n=16). The patients of the different samples were chosen randomly from different groups by random number generation with the help of a sub-programme of statistic programme SPSS/PC v 5.01 (SPSS Inc, Chicago, USA). Patients with IA-A and IA-G were chosen from the general series of IA reported above. Both the atopic patients and those with urticaria, were selected from those patients who attended our Allergy Unit during two months in 1995 (February and March). The healthy subjects were those who attended the Allergy Unit for drug hypersensitivity evaluation, during the same months of 1995, and after being examined, showed neither drug hypersensitivity, nor atopy nor any history of urticaria. Given that codeine is a secretagogue of mast cells, and thereby a histamine releaser [14], we

endeavoured to establish whether the reactions obtained by codeine depended on the cutaneous reactions to histamine, and for this purpose the response to histamine by skin prick test was also studied in the same groups of patients [8]. No differences were observed in the five groups, neither in mean age (variance analysis,  $p=0.94$ ) or in the distribution of sexes ( $p=0.54$ ). In reference to patients exhibiting IA-G, those who had simple episodes of urticaria (urticaria without hypotension or digestive or respiratory signs or symptoms) were excluded so as to rule out that the possible enhanced cutaneous reaction to codeine was due to urticaria, an entity in which an enhanced mast cell releaseability has been described [8]. Patients with simple episodes of urticaria were not withdrawn from the group IA-A due to the presence of urticaria in 80% of the cases of this sub-type of IA. The study was approved by the Research Committee of Hospital General de Albacete.

### Definitions

*Idiopathic anaphylaxis:* Although the lack of skin involvement during episodes of anaphylaxis does not preclude anaphylaxis, when there is no identifiable cause, as in IA, it is difficult to differentiate anaphylaxis from other illnesses that may simulate anaphylaxis when there are no cutaneous symptoms. For this reason, we followed the definition of IA published by Choy et al [9]. According to those authors, this condition refers to the syndrome of idiopathic urticaria or angioedema with at least one of the following symptoms: collapse, shock, bronchospasm or upper airway symptoms, gastrointestinal symptoms including pain and acute diarrhea, such that a potentially life-threatening medical emergency occurs. Upper airway symptoms can produce pharyngeal or uvular edema or acute laryngeal swelling, resulting in voice change (hoarseness documented by patient or family or a physician) or documented vocal cord swelling. In addition, we distinguish two sub-types within the clinical picture of IA: Generalized Idiopathic Anaphylaxis (IA-G), when the symptoms or signs of urticaria or angioedema are associated to the lower airways, or gastrointestinal or cardiovascular symptoms or signs, and Idiopathic Anaphylaxis with Angioedema (IA-A), when the symptoms or signs of urticaria, or angioedema are accompanied by upper airways symptoms only.

*Urticaria:* In this paper we will use the term urticaria to refer to patients who have only urticaria without other symptoms or signs of respiratory, digestive or cardiovascular system involvement. When we use urticaria as symptom of an episode of anaphylaxis, we will say symptoms or signs of urticaria.

Therefore, in this study, according to these authors, if a patient with urticaria had signs or symptoms of upper airway involvement, we consider that these patients had idiopathic anaphylaxis with angioedema (IA-A).

Table 1. Comparisons of quantitative variables between patients with IA-A and IA-G

Variable	IA Subtype	N	Mean± standard deviation	Median	Range	p between IA-G and IA-A
N° Episodes in the year of greatest frequency	IA	81	5.72±14.74	2	1-130	0.03
	IA-G	55	7.01±17.63	3	1-130	
	IA-A	26	3±3.44	2	1-15	
N° Visits to Emergency Unit in the year of greatest frequency	IA	75	2.84±4.34	2	0-24	0.01
	IA-G	50	3.58±5.11	2	0-24	
	IA-A	25	1.36±0.81	1	0-3	
Total IgE U.I./mL	IA	75	211.17±313.73	87	2-1793	0.0052
	IA-G	50	268.88±364.67	135	2-1793	
	IA-A	25	95.76±105.55	62	2-402	
Eosinophils per µL in serum	IA	77	208.88±194.91	150	10-1150	0.13
	IA-G	52	220.17±177.9	165	20-730	
	IA-A	25	185.4±228.44	140	10-1150	
Basophils per µL in serum	IA	75	40.68±21.28	40	10-110	0.01
	IA-G	51	45.11±22.04	40	10-110	
	IA-A	24	31.25±16.23	30	10-60	
C3 mgr/dl	AI	75	83.29±15.16	82	43-123	0.91
	AI-G	53	83.41±15.7	83	43-123	
	AI-A	22	83±13.94	82	45-117	
C4 mgr/dl	AI	75	37.83±12.66	35	10-71	0.63
	AI-G	53	38.28±12.63	36	10-71	
	AI-A	22	36.72±12.94	32	20-65	

(IA) Idiopathic Anaphylaxis, (IA-A) Idiopathic Anaphylaxis with Angioedema and (IA-G) Generalized Idiopathic Anaphylaxis

## Techniques

*Cutaneous tests with histamine and codeine:* Four different and consecutive concentrations (factor of 3) were used both for histamine as well as for codeine (Stallergens, Fresnes, France). The initial concentration of histamine was 10 mg/ml and 90 mg/ml for codeine. The skin tests were performed by means of a skin Prick test [10], using a Prick Lanceter (DHS BAYER, Química Farmacéutica Bayer, Valdemoro, Madrid). The different concentrations, duplicated, were carried out on the anterior part of the forearm, and their positions were determined by randomisation in accordance with a Latin square [11]. The cutaneous response studied was the wheal area which was read in 15 minutes, sketching the contours formed using a same type of marker and then transferred to a transparent tape. This tape was

subsequently glued to a page for its subsequent digital scanning. Finally, each wheal area was measured by means of planimetry using the Autocad programme. Both the prick test as well as the wheal area reading were carried out blindly on clinical characteristics of patients by the investigator who performed both proceedings (M.A.T.A.).

## Statistics

A logistic regression model was created to know if there were differences between IA-G and IA-A using those variables of greater clinical and/or statistical significance in the univariate analysis. The univariate analysis, in the case of qualitative variables, was carried out with  $\chi^2$  or two-tailed Fisher Exact Test, and for quantitative variables with t-Student or U of Mann-

Table 2. Comparisons of quantitative variables between patients with Idiopathic Anaphylaxis with Angioedema (IA-A) and Generalized Idiopathic Anaphylaxis (IA-G)

Variable	IA-G		IA-A		p	O.R. with 95% C.I
	N	%	N	%		
% Women	55	37 67.3%	26	18 69.2%	0.86	0.91 (0.33-2.49)
Urban Environment	55	29 52.7%	26	12 46.2%	0.58	1.30 (0.46-3.68)
Use of Steroids	55	20 36.4%	25	4 15.4%	0.053	3.14 (0.94-10.42)
Remission	52	39 75%	22	17 77.3	0.83	0.88 (0.21-3.20)
Anaphylaxis of known origin	55	10 18.2	26	1 3.8%	0.09	5.55 (0.67-45.95)
Exercise Anaphylaxis	55	7 12.7	26	1 3.8%	0.21	3.65 (0.42-170.78)
Atopic diseases	55	33 60%	26	6 23.1%	0.0019	5 (1.73-14.43)
Food allergy	55	13 23.6%	26	3 11.5%	0.20	2.37 (0.61-9.19)
Urticaria or angioedema	55	26 47.3%	26	21 80.8%	0.0043	0.21 (0.07-0.64)

(IA) Idiopathic Anaphylaxis, (IA-A) Idiopathic Anaphylaxis with Angioedema and (IA-G) Generalized Idiopathic Anaphylaxis

Witney, according to the usual recommendations for the use of these statistical tests. The SPSS/PC+5.1 software (SPSS Inc. Chicago. USA) was employed for these statistical techniques [12].

Analysis of the different wheal areas produced by histamine and codeine in the different study groups was carried out by means of a parallel line assay, after observing that the distributions fulfilled the conditions of normality, linearity and parallelism [11]. A logarithm 10 was applied to the different areas produced by the different concentrations. If the conditions of linearity and parallelism were not fulfilled, a multivariate analysis of the variance (Hotelling's T2 test) was then applied. Parameters of cutaneous tolerance Index (CTI) were included in the analysis of parallel lines. CTI is the number of times in which it is necessary to multiply the concentrations of an extract, in order to obtain the same wheal areas as those obtained by the same concentrations of another extract. The PLA programme PLA (ALK-

Abelló, Madrid) [13] was employed to perform the parallel line assay.

Those analyses with a p less than 0.05 were considered significant.

## Results

### Clinical differences between IA-A and IA-G patients

Among the 81 IA patients, 55 patients (67.9%) had IA-G, whereas 26 patients (32.1%) exhibited IA-A. All patients with IA in our series had no severe involvement of upper airways such as massive tongue or pharyngeal swelling or stridor. The most important data from the univariate analysis appear in Table 1 and 2. The greater presence of atopic diseases, exercise induced anaphylaxis and food allergy among those patients with

**Table 3.** Data of the logistic regression equation of having IA-G when one has Idiopathic Anaphylaxis (IA): Total IgE favoured the presence of IA-G, while urticaria did not favour it.

Variable	$\beta$	p	ODDS Ratio	O.R. with 95% C.I.
Constant	1.0522	0.077		
Total IgE	0.0066	0.016	1.006	1.001-1.010
Urticaria	-1.8826	0.0043	0.159	0.040-0.507

(IA) Idiopathic Anaphylaxis, (IA-A) Idiopathic Anaphylaxis with Angioedema and (IA-G) Generalized Idiopathic Anaphylaxis

IA-G are noteworthy. Various models of logistic regression were created to know if there were differences between both subtypes of IA. Of all the equations of logistic regression tested, the equation with the greatest efficacy, for classifying patients of both groups, was that one in which total IgE favoured the presence of IA-G, with an O.R. of 1.006; whereas the presence of episodes of urticaria did not favour IA-G with an O.R. of 0.159 (in other words urticaria favoured the presence of IA-A). Seventy five percent of the total cases analysed were classified by this model with 82.2% for IA-G and 60.8% for IA-A (Table 3).

## Mast cell releasability

As to the analysis of cutaneous reactivity to codeine, it was performed by matching pairs from each group (IA-G with IA-A, IA-G with atopy, IA-G with urticaria, IA-A with atopy...) so as to complete all the matching possibilities. The lines of IA-G on one hand, and those from atopic patients and urticaria on the other, did not fulfil the criteria of parallelism. The differences between lines in patients with IA-G and healthy controls ( $p=0.19$ ) (Table 4) and patients with IA-A and IA-G ( $p=0.81$ ) were not statistically different. However, statistical differences existed between patients with IA-G and atopy (Hotelling's T2 test,  $p=0.0053$ ). In this case, the mean vectors being greater in patients with IA-G (Table 5). Statistical significance was observed between IA-G and urticaria (Hotelling's T2 test,  $p=0.048$ ). However, in this case, the mean vectors were greater in those patients with urticaria (Table 5).

In reference to the analysis of the lines produced by IA-A on one hand and atopic patients, patients with urticaria and healthy subjects on the other, all the lines fulfilled the conditions of parallelism except those of IA-A and urticaria. When the lines of IA-A and healthy subjects were compared, no differences could be observed ( $p=0.12$ ). However, significant differences were observed in the lines produced by IA-A and atopic patients ( $p=0.017$ ), thereby IA-A patients showing a

**Table 4.** Data of parallel line assays. Urticaria variable was controlled for the case of IA-G

Lines compared (1 versus 2)	Variance Analysis		Cutaneous tolerance index (CTI) with 95% C.I.
IA-G Versus IA-A	F ratio = 0.053	p= 0.81	0.78 (0.01-28.21)
IA-G Versus atopic disease	Conditions of linearity and parallelism were not fulfilled		
IA-G Versus urticaria	Conditions of linearity and parallelism were not fulfilled		
IA-G Versus healthy controls	F ratio = 1.69	P = 0.19	3.35 (0.49-519.90)
IA-A Versus atopy	F ratio = 5.79	p = 0.017	3.08 (1.22-10.91)
IA-A Versus urticaria	Conditions of parallelism were not fulfilled		
IA-A Versus healthy controls	F ratio = 2.33	p = 0.12	3.30 (0.70-72.19)
Urticaria Versus atopy	F ratio = 4.18	p = 0.04	1.96 (1.02-4.17)
Atopy versus healthy controls	F ratio = 0.03	p = 0.85	0.92 (0.33-2.51)

(IA) Idiopathic Anaphylaxis, (IA-A) Idiopathic Anaphylaxis with Angioedema and (IA-G) Generalized Idiopathic Anaphylaxis

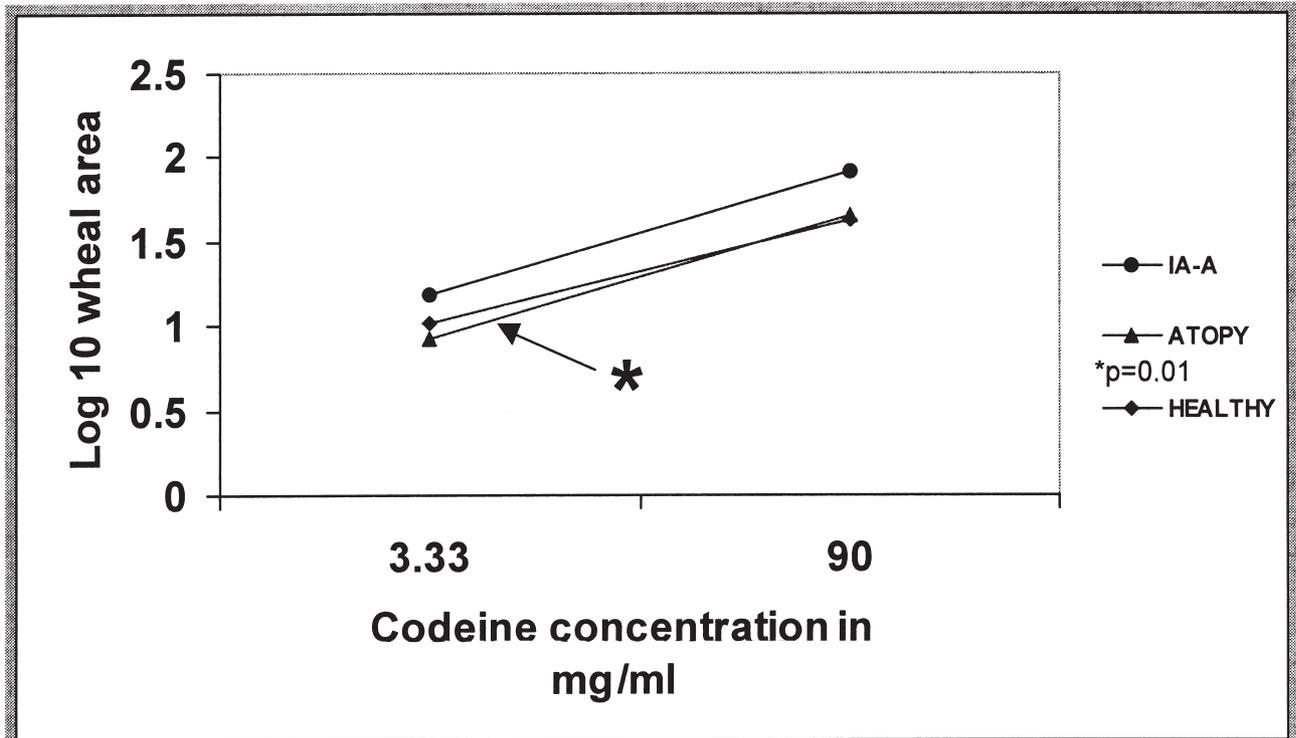


Figure 1. Parallel line assay with codeine comparing the IA-A line with the rest of lines of other populations. Without asterisk line with no difference. Idiopathic Anaphylaxis (IA-A).

Table 5. Data of Hotelling's T<sup>2</sup> with codeine, comparing cutaneous reactions in different populations one by one. Urticaria variable was also controlled in the case of IA-G

Groups to compare	Mean of vectors with 90 mg/ml	Mean of vectors with 30 mg/ml	Mean of vectors with 10 mg/ml	Mean of vectors with 3 mg/ml	Hotelling's T <sup>2</sup>	F ratio	p
IA-G	1.66	1.67	1.23	1.53	18.74	4.26	0.0053
Atopic illness	1.71	1.44	1.22	0.78			
IA-G	1.66	1.67	1.23	1.53	11.59	2.62	0.048
Urticaria	1.91	1.72	1.58	0.78			
IA-A versus	1.71	1.61	1.67	1.20	8.85	1.94	0.14
Urticaria	1.91	1.72	1.58	0.78			

(IA) Idiopathic Anaphylaxis, (IA-A) Idiopathic Anaphylaxis with Angioedema and (IA-G) Generalized Idiopathic Anaphylaxis

Table 6. Correlations of the reactions to codeine and to histamine in patients with Idiopathic Anaphylaxis

histamine/codeine Concentrations	Correlation (Pearson)	Lineal regression
Histamine = 0.37 mgr/mL Codeine = 3.33 mgr/mL	r = 0.072 p = 0.54	
Histamine = 1.11 mgr/mL Codeine = 10 mgr/mL	r = 0.54 p < 0.001	F = 29.25 p < 0.0001 R <sup>2</sup> = 0.29
Histamine = 3.33 mgr/mL Codeine = 30 mgr/mL	r = 0.35 p = 0.003	F = 9.81 p = 0.002 R <sup>2</sup> = 0.11
Histamine = 10 mgr/mL Codeine = 90 mgr/mL	r = 0.35 p = 0.002	F = 12.93 p = 0.0006 R <sup>2</sup> = 0.14

greater cutaneous response to codeine than atopic patients (figure 1). The Hotelling's T2 test showed no significant differences between patients with IA-A and those with urticaria (p=0.14).

As codeine is a secretagogue of mast cells, and so a histamine releaser [14], we endeavoured to establish whether the reactions obtained by codeine depended on the cutaneous reactions to histamine, and for this purpose we assessed whether a correlation existed between the wheal areas obtained by different histamine concentrations and codeine. Correlations were made on a one-by-one basis between maximum, intermediate and minimum concentrations of codeine and histamine. Except for the correlation between codeine (3 mg/ml) and histamine (0.3 mg/ml) which was not significant (r=0.07, p=0.54), the remaining correlations between maximum, minimum and intermediate were significant. However, these reactions to histamine explained only 29% of codeine variance (range between 0.11 to 0.29) (Table 6).

## Discussion

Since 1989, Idiopathic Anaphylaxis has been divided into Generalized Idiopathic Anaphylaxis (IA-G) and Idiopathic Anaphylaxis with Angioedema (IA-A) [1,2]. With respect to clinical differences between these two sub-types, we observed in the different models of logistic regression tested in this study, that patients with IA-G seem to be closely related to the presence of atopy (higher IgE, a greater presence of atopic diseases), whereas patients with IA-A are closely related to the presence of urticaria. In addition, IA-G and IA-A patients showed a different response to codeine in our

study: while IA-G patients showed a lower reaction to codeine than the controls with urticaria, patients with IA-A do not differ from the controls with urticaria in their reaction to codeine.

Although a cut-off point does not exist in clinical practice that separates total IgE values of atopic and non-atopic patients [15], in several epidemiological studies the patients with higher total IgE showed a greater percentage of sensitisation to common inhalant allergens [16-19].

In spite of a similar prevalence of atopy among IA patients from the series of the North Western University group (NU) of Chicago (43 to 48%) [20, 21] and our own (48%) in the NU group no differences were observed in the prevalence of atopy between IA-G and IA-A patients [22]. The difference is not attributable to different definitions, and those used in this study are the same used for this group. It may be that the different prevalence of atopy among IA-A patients reflects different prevalences among the respective populations studied [22]. However, in our IA-A patients, as in the cases of IA-A of the NU, the prevalence of atopic disorders was greater than those of the general populations studied (in our series 23.07% in IA-A opposed to 9.43% of the Albacete general population; whereas in the series of NU the prevalence of atopy was 40.5% among patients with IA-A, which was greater than that of the general population studied [21]). Consequently, the reasons for these discrepancies are unknown to us.

The form in which total IgE and atopy play a determining role in the appearance of Generalized IA (IA-G) cannot be established in this study. It may be related to some of the more significant findings observed among IA-patients, such as increased prevalence of food

allergy (19.8%), or the presence of exercise-induced anaphylaxis (12.7%), diseases in which a high prevalence of atopy has been observed [23, 24]. In these diseases an enhanced basophil releasability has been observed in the case of food allergy [25], and cutaneous mast cell releasability after exercising and specific food intake that promotes these episodes in the case of food-dependent exercise induced anaphylaxis [26, 27]. It is possible that enhanced mast cell and basophil releasability in atopic patients are the basis for explaining IA-G episodes.

Some allergists are of the opinion that if in patients with IA, some of the episodes of anaphylaxis are due to a known cause (food, drugs...), these patients should not be labeled as idiopathic anaphylaxis. However, like the Northwestern University Group of Chicago [20], we believe that a particular patient may have both types of anaphylaxis (idiopathic and non-idiopathic). Firstly, both patients and allergists make a clear distinction between episodes that occur either after exercise or immediately after food consumption and those episodes with no apparent cause. In addition, we classified all episodes of anaphylaxis according to the most widely accepted criteria in order to establish a cause-effect relationship between a cause and an episode of anaphylaxis (discussed previously in another paper [6, 28, 29, 30]). Therefore, if these criteria had not been applied and we had excluded patients with episodes of anaphylaxis of known and unknown cause, we would probably have introduced a selection bias.

Sonin [4] did not prove that basophils from IA patients released more histamine spontaneously or after being stimulated with anti-IgE, than basophils from non-atopic patients. Probably, basophils are not good candidate cells for studying a recurrent and acute disorder such as IA. It is well known that basophils are implicated in the late phase of the allergic reaction and in the chronic stage of the allergic process [31-33]. Consequently, we thought that the best cells to study IA were mast cells [34].

In our series, we analysed mast-cell releasability by means of cutaneous reaction to codeine in IA-G patients, IA-A, atopic controls, healthy subjects and those with urticaria. Among the different forms of studying mast cell releasability, this is a simple and non-aggressive method.

In our study, we observed that IA-G patients showed a greater reaction to codeine than atopic patients. This difference cannot be explained simply by a different skin sensitivity of these patients to histamine released after administering codeine; histamine explained only 12-29% of the variability obtained by codeine, in alignment with other reports which also show a cutaneous reaction to opiate substances that does not depend exclusively on the reaction to histamine [3, 7, 14]. Another alternative explanation for these data is the presence of different amounts of mast cells in patients' skin of the different groups. Garriga described a small but

significant increase of mast cells in the skin of IA-G patients with respect to healthy subjects [35]. Although cutaneous biopsies in the tested groups were not conducted in this study, Khefer [5] did not find in mastocytosis, a disease with a significant increase of mast-cells in skin, that the wheal and erythema areas produced by morphine were greater in these patients compared to healthy subjects. Likewise, the increase of mast-cell releasability, described in patients with urticaria, is based on healthy skin, in which the number of mast cells is normal. Therefore, the most feasible explanation for the data is that our IA-G patients seem to have a greater releasability (or threshold decrease to produce the release of mediators) than that of atopic patients, although less than those patients with urticaria, and not different from healthy subjects and patients with IA-A.

For some authors, the diagnosis of anaphylaxis can only be made if there is a life-threatening involvement of target organs (upper airways, heart...). For instance, they consider that if a patient with urticaria reports mild symptoms of upper airway involvement as tongue swelling or voice change, this patient must be labelled as urticaria, and only if there is severe obstruction of the upper airways requiring intubation, this patient with urticaria must be classified as IA. However we think that there is not enough evidence that allows us to establish whether a patient is suffering from anaphylaxis or urticaria according to the severity of upper airway involvement. On the other hand, it would be difficult to establish the degree of upper airway obstruction which separates urticaria from anaphylaxis. These are the reasons why many authors consider the diagnosis of anaphylaxis when there is a clinical picture suggestive of mediator discharge from mast cells, the symptoms being mild or severe. This is the position of Northwestern University when they diagnose IA, and it is the same position chosen by us, in our study to separate urticaria from anaphylaxis.

The IA-A and urticaria groups had a very similar behaviour. Both groups had cutaneous reactions to codeine greater than that of atopic patients and not different from healthy subjects. No differences were observed between patients with IA-A and urticaria. However, there were significant differences between patients with IA-G and urticaria ( $p=0.048$ ), but not between IA-G and IA-A. On the other hand, there was an association between IA-A and urticaria in the logistic regression study which was used to study clinical differences between the different sub-types of IA. The fact that IA-G patients are different from patients with urticaria, but not from IA-A patients, seems to involve a contradiction and this could be related to the greater presence of acute urticaria among IA-A patients, than among those with urticaria (data not shown). It has been proven that patients with chronic active urticaria exhibit greater histamine release than chronic urticaria patients in remission (at least 6 months without remission).

Therefore, the enhanced mast cell releasability produced in urticaria may be transient [36]. If we assume that patients with acute urticaria have longer periods of remission than those with chronic urticaria, then any diminution in mast cell releaseability due to the fact that urticaria is in a silent phase may explain that there are differences between IA-G and urticaria but not between IA-G and IA-A.

These facts could lead us to consider whether Idiopathic Anaphylaxis with angioedema (IA-A) should be separated from anaphylaxis syndrome, and to be considered as an illness more closely related to urticaria, and therefore to use the Idiopathic Anaphylaxis term only in those patients with a generalized type of anaphylaxis of unknown cause. Perhaps a study which assesses if the IA-A group has the same behaviour as urticaria with other parameters, such as increased presence of IgG antibodies against FcεRI [37], reduced number of basophiles in serum [38] or defective histamine release of basophiles [39] (findings reported in chronic idiopathic urticaria), would provide additional evidences in favour of showing that urticaria and IA-A are related illnesses.

In conclusion, IA as defined in the first paragraphs of this paper, seems to be a heterogeneous entity, in its clinical manifestations and its response to codeine: IA-G appears more frequently among atopic patients than in IA-A patients. Enhanced mast cell releaseability may be one of the reasons among others yet unknown, of the presence of IA-G among patients with atopy. On the other hand, IA-A patients and urticaria patients showed very similar skin responses to codeine, and so together with its association with urticaria in the logistic regression model employed, led us to believe that both entities are closely related or they are the same illness with different grades of severity or organ involvement.

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