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Subtypes of chronic Urticaria in patients attending allergy clinics in Venezuela

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Summary
Chronic urticaria (CU) is one of the most puzzling clinical entities confronted by the medical profession. It is a common motive for consultation, and in a sizable proportion of patients no identifiable cause is evident. Since there are relatively few publications regarding CU in developing countries, we performed a prospective 3-year study on the demographic and clinical features of patients with CU.
Four hundred and twenty-three subjects were studied, 52 children and 371 adults, 295 females (69.7%), with a mean age of 38.4 ± 17.8 years. More often, wheals and angioedema (AE) were present on the head, upper and lower limbs and the trunk. AE was present in 162 patients (38.4%). The most frequent subtypes were chronic spontaneous urticaria, aspirin-exacerbated cutaneous disease, dermographic urticaria, and combinations of various subtypes.
A better understanding of the characteristics of patients suffering CU is helpful for clinicians dealing with this ailment, and provides guidance for new investigations on its pathogenesis, which will hopefully result in a better management of this vexing condition.

Introduction

Chronic urticaria (CU) constitutes one of the most challenging medical conditions in allergology. It is a common cause for consultation, with lifetime prevalence rates in the general population of up to 1.8% (1). The disease compromises patient's quality of life (2,3), decreases productivity and demands substantial resources from health services (4), and in many cases does not respond to the best available treatment.

The management of patients suffering CU may be difficult due to present limitations to fully understand its pathogenesis (5), and in consequence to obtain an etiologic diagnosis, since in a large number of cases no detectable external or internal factors are the cause of the wheals, and urticaria is labelled as spontaneous.

CU affects patients from all age groups, and it may involve any areas of the skin as well as mucosal tissues in the form of angioedema (AE) of the upper respiratory and gastrointestinal tracts. When an etiologic agent is present, it is generally related to physical agents (pressure, cold, heat, sunlight, vibration), drugs, foods, contactant allergens, insect stings, or emotional stress. Among internal factors, chronic infections (for example, *Helicobacter pylori*) (6) and autoimmunity (7) are mentioned.

There are few studies in the literature on the demographic and clinical features of patients with CU, and the prevalence of CU subtypes is largely unknown, especially in developing countries. In this investigation we aimed to study prospectively patients with CU/AE observed in outpatient allergy clinics from Caracas, Venezuela, during a three-year period of observation. We regard these observations as very useful for clinicians taking care of patients suffering this common disease around the world, and more especially in developing areas of the world.

Materials and methods

This investigation is a prospective study, which included all new patients with CU of any age or sex, attending two allergy outpatient clinics in Caracas, Venezuela, between January 1st, 2010, and December 31st, 2012. Written informed consent was obtained from patients for inclusion into the study, and the protocol was approved by the Institutional Review Board from Clínica El Avila.

Data on age, gender, duration of symptoms, body distribution of wheals, triggering factors, previous and concomitant medical history, were obtained by direct questioning and physical examination done by an allergist. The following laboratory investigations and immediate-type skin prick tests with inhalant and food allergens were done in selected patients according to the information derived from the medical history and patient's examination: complete blood cell and differential leukocyte count, thyroid function tests, antinuclear and anti-thyroid antibodies, erythrosedimentation rate, C-reactive protein, serology for *H. pylori*, *Mycoplasma pneumoniae* and syphilis, total serum IgE, blood chemistry, urine and stool analysis.

CU was defined according to current International Guidelines as the appearance of wheals and/or AE lasting longer than 6 weeks (8). Subtypes of CU included spontaneous, physical, cholinergic, aquagenic, and contact urticaria. A subset of patients with chronic spontaneous urticaria (CSU) who experienced disease exacerbations when exposed to aspirin or nonsteroidal anti-inflammatory drugs that inhibit COX-1 isoenzyme of arachidonic acid metabolism (NSAIDs), were designated as having aspirin-exacerbated cutaneous disease (AECD) (9,10). Autoreactivity was confirmed in patients who showed a positive autologous serum skin test (11). Some patients exhibited combinations of various urticarial subtypes.

The treatment of CU was done following recommendations from EAACI/GA(2)LEN/EDF/WAO guidelines (12), which include second generation, nonsedating, anti-H1 antihistamines, with the addition of short courses of systemic corticosteroids for exacerbations, and leukotriene-receptor antagonists, immunosuppressants, or omalizumab in patients not responding to antihistamines at conventional or higher doses.

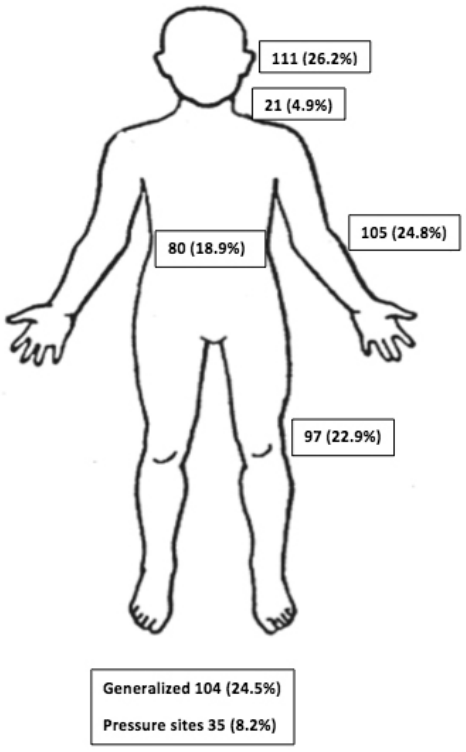
Results

During the lapse 2010-2012, 423 new patients with CU were studied. Fifty-two were children and adolescents (2 to 18 years) (12.2%) and 371 were adults (> 18 years) (87.7%), 295 females (69.7%) and 128 males (30.2%). Mean age was 38.4 ± 17.8 years (range 2-85 years) and mean disease duration was 28.2 ± 63.3 months (range 2-540 months).

Previous and concomitant medical history is shown in **table 1**, where it can be observed that most common associated diseases were allergic rhinitis, asthma, hypertension, thyroid diseases, chronic rhinosinusitis, and nephrolithiasis, while the frequency of other conditions was not increased.

Body distribution of the wheals and AE is presented in **figure 1**. Most common sites were the head (including facial AE), upper and lower limbs, and the trunk. Generalized urticaria was present in 24.5% of patients, and wheals on sites of pressure on the skin in 8.2%. AE was present in 162 patients (38.4%), with 61.4% showing exclusively urticaria, 26.0% urticaria and AE, and 12.4% AE alone.

Figure 1 *- Distribution of wheals and angioedema in 423 patients with chronic urticaria.*



The following precipitating factors were suspected from patient questioning: drugs (7.3%), foods (1.1%), and physical agents (12.9%). Less frequent inducers were emotional stress, insect stings, exercise, pets, house dust, and contact allergens (**table 2**). No specific triggers were identified by 318 patients (75.2%).

Table 3 presents the results of laboratory investigations done in 166 patients. Abnormal results were obtained in 80 (48.1%), and normal tests in 86 (51.8%). Most frequent abnormalities were blood eosinophilia, increased total serum IgE, and anti-thyroid autoantibodies. The autologous serum skin test

Table 1 *- Previous and concomitant diseases in 423 patients with chronic urticaria.*

Disease	n (%)	Disease	n (%)	Disease	n (%)
Allergic rhinitis	86 (20.3)	Diabetes mellitus	3 (0.7)	Hyperuricemia	1 (0.2)
Asthma	51 (12.0)	Fixed drug eruption	2 (0.4)	Hodgkin's disease	1 (0.2)
Thyroid disease	33 (7.8)	Atopic dermatitis	2 (0.4)	Non-Hodgkin's lymphoma	1 (0.2)
Hypertension	26 (6.1)	Chronic renal failure	2 (0.4)	Erythema nodosum	1 (0.2)
Chronic rhinosinusitis	17 (4.0)	Brain dysrhythmia	2 (0.4)	Chronic cystitis	1 (0.2)
Nephrolithiasis	11 (2.6)	Celiac disease	2 (0.4)	Psoriasis	1 (0.2)
Vitiligo	5 (1.1)	Systemic lupus erythematosus	2 (0.4)	Gilbert's disease	1 (0.2)
Migraine	4 (0.9)	Autoimmune hemolytic anemia	1 (0.2)	Hyperlipemia	1 (0.2)
Gastritis	3 (0.7)	Brain aneurism	1 (0.2)	-	-
Hyperinsulinism	3 (0.7)	Berger's disease	1 (0.2)	-	-

Table 2 *- Agents inducing wheals in 423 patients with chronic urticaria.*

Drugs (n = 31, 7.3%)		Miscellaneous (n = 69, 16.3%)		Foods (n = 5, 1.1%)	
NSAIDs	18 (4.2)	Pressure	45 (10.6)	Shellfish	3 (0.7)
ACE inhibitors	5 (1.1)	Sunlight	7 (1.6)	Milk	1 (0.2)
Radiocontrast media	2 (0.4)	Emotional stress	6 (1.4)	Fish	1 (0.2)
Oral contraceptives	1 (0.2)	Cold	3 (0.7)	-	-
Glyburide/ metformin	1 (0.2)	Exercise	2 (0.4)	-	-
Losartan	1 (0.2)	Insects	2 (0.4)	-	-
Penicillin	1 (0.2)	Cat	1 (0.2)	-	-
Lorazepam	1 (0.2)	Dog	1 (0.2)	-	-
Oxcarbazepam	1 (0.2)	House dust	1 (0.2)	-	-
-	-	Contact with cosmetic	1 (0.2)	-	-

(ASST) was done in 12 patients and all of them showed positive responses, whereas ASST was negative in 10 control individuals who did not have urticaria.

Immediate-type skin prick tests with allergens were done in 256 patients (60.5%), with positive results to at least one allergen in 157 (61.3%), and negative tests in 99 (38.6%). Cutaneous tests with *Dermatophagoides pteronyssinus* were positive in 125 patients (48.8%), *Blomia tropicalis* in 121 (47.2%), *Dermatophagoides farinae* in 54 (21.0%), American cockroach in 42 (16.4%), dog in 40 (15.6%), cat in 33 (12.8%), and moulds in 18 (7.0%). Skin tests with food extracts were positive in 36 patients (14.0%), including shellfish in 14 (5.4%), and mixed fish in 11 (4.2%) (data not shown).

The subtypes of CU in the studied population are depicted in **table 4**. Chronic spontaneous urticaria (CSU) was present in 294 patients (69.5%), followed by dermographic urticaria (14.4%). U/AE induced by drugs (excluding NSAIDs) was present in 3 patients (0.7%). In patients with CSU, 49 (16.6%) had disease exacerbations after taking NSAIDs (AECD), 12 had CAIU, and 24 (5.6%) showed combinations of various subtypes of urticaria.

Table 3 *- Abnormal laboratory results in 166 patients with chronic urticaria.*

Test	n (%)	Test	n (%)	Test	n (%)
Blood eosinophilia	19 (11.4)	Increased CRP	4 (2.4)	Increased alkaline phosphatase	1 (0.6)
Increased serum IgE	19 (11.4)	Positive serology for *H. pylori*	3 (1.8)	Increased T3	1 (0.6)
Anti-thyroid antibodies	14 (8.4)	Hyperuricemia	2 (1.2)	Decreased TSH	1 (0.6)
B. hominis in stools	7 (4.2)	Increased lactate dehydrogenase	1 (0.6)	Decreased T4	1 (0.6)
Increased ESR	6 (3.6)	Microscopic hematuria	1 (0.6)	Positive serology for syphilis	1 (0.6)
Antinuclear antibodies	5 (3.0)	Positive serology for *M. pneumoniae*	(0.6)	*A. lumbricoides* in stools	1 (0.6)
Increased aminotransferases	5 (3.0)	Proteinuria	1 (0.6)	*G. lamblia* in stools	1 (0.6)
Increased TSH	4 (2.4)	Bacteriuria	1 (0.6)	-	-

ESR: erythrosedimentation rate; TSH: thyro-stimulating hormone; CRP: C-reactive protein; T3: tri-iodothyronin; T4: Thyroxine.

Table 4 *- Subtypes of chronic urticaria.*

Subtype	n	%
Chronic spontaneous urticaria (CSU)[1]	294	69.5
Dermographic urticaria	61	14.4
Autoimmune urticaria (CAIU)	12	-
AE induced by ACE inhibitors	7	1.6
Papular urticaria	6	1.4
Solar urticaria	5	1.1
Mastocytosis	3	0.7
Cholinergic urticaria	2	0.4
Cold-induced urticaria	2	0.4
Delayed pressure urticaria	1	0.2
Contact urticaria	1	0.2
Losartan-induced AE	1	0.2
Oxcarbazepine-induced urticaria	1	0.2
Aquagenic urticaria	1	0.2
Candesartan-induced urticaria	1	0.2
Urticarial vasculitis	1	0.2
Combinations[2]	24	5.6

[1]Includes 49 patients with aspirin-exacerbated cutaneous disease (AECD). [2]Combinations: CSU and dermographic urticaria (18), CAIU and AECD (3), CSU and dermographic and cold-induced urticaria (1), CSU and solar urticaria (1), dermographic and solar urticaria (1).

Discussion

Since there are unmet needs to fully understand CU, especially in regard to its pathogenesis and management, this disease remains an important challenge for clinicians and particularly for allergists and dermatologists. We have performed this investigation in order to contribute to the knowledge of the clinical features of CU in patients seen in allergy clinics from a developing country.

Although CU may affect patients of any age or sex, in the present study it was observed more often in young adults, with predominance in women. The duration of the disease was highly variable, with some subjects suffering from recurrent wheals for many years (up to 45 years). In the subset of patients who were submitted to skin tests, it was observed that 61% were atopic, about 20% had a history of allergic rhinitis and 12% of asthma. Another associated disease common in these patients was autoimmune thyroid disease, as has been described by other authors (**table 1**) (13). AE, especially of the face and upper respiratory tract, was present in 38.4%, a proportion similar to the prevalence reported by other investigators (reviewed in reference (14)).

An environmental inducing agent was suspected only in 24.8% of patients, while in 75.2% there were no evidences suggesting a cause for symptom occurrence (**table 2**). In most cases laboratory investigations did not contribute to the diagnosis (**table 3**). This confirms the recommendations of the International Guidelines on indicating complementary tests only in selected patients, guided by the information derived from the medical history and physical examination (8).

A high proportion of our patients were labelled as having CSU. Within this group, AECD and combinations with physical urticarias were common. In a review article by Maurer et al 66-93% of patients with CU had CSU, 4-33% physical urticaria, 1-7% cholinergic urticaria, and the frequency of identification of the cause of CU varied between 0% and 43%, with a higher percentage in studies that included the ASST (14).

In the group of physical urticarias, dermographic urticaria was the most common, whereas drug-induced and food-induced urticarias were relatively infrequent. This observation is clinically important, since most patients and some physicians often believe that CU is due to food allergy. We did not explore the possibility of food additives as inducers of urticaria, because this task deserves additional study using a specially designed protocol (15). However, not all experts are convinced on the causal relationship between pseudoallergens and CU (16).

Although insect stings induce more often acute urticaria, especially in children, we observed 6 patients with chronic urticaria related to chronic exposure to mosquitoes. Papular urticaria (prurigo) is not generally included in the classification of urticaria, because in most developed countries from Europe and North America this condition is not commonly observed. It is, however, an important condition in developing countries from tropical and subtropical regions (17).

In conclusion, CU is one of the most difficult-to-manage illnesses in allergy and dermatology. We have observed that CU is more frequent in young adult females. Lesions are more often present on the head, upper and lower limbs and the trunk. AE is present in almost 40% of patients, and the most frequent CU subtypes are chronic spontaneous urticaria, aspirin-exacerbated cutaneous disease, dermographic urticaria, and combinations of various subtypes.

Present results will be helpful for clinicians in general and specialized practitioners, and will give new clues for additional investigations on the pathogenesis of CU, which hopefully will provide strategies for a better management of this condition.

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