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Chronic spontaneous urticaria is not an allergic disease

The links between chronic urticaria, IgE sensitization and allergy have been much discussed but little studied. We investigated IgE sensitization and allergy in 128 adult chronic urticaria patients during 2006-2008. During a one-day hospitalisation, the patients answered a standardized questionnaire and underwent blood serum analysis, physical tests and skin prick-tests. IgE sensitization to environmental allergens was defined by the positivity of at least one skin prick test and/or elevated levels of serum IgE ≥ 300 KUI/L. The chronic urticaria was considered allergic if: i) a high correlation between positive skin prick tests to a clinically relevant allergen and the case history was found; ii) complete remission of urticaria occurred within two months of allergen withdrawal. Of 105 patients with interpretable skin prick tests, 46.7% were IgE sensitized. Two patients had clinically relevant positive skin prick tests but their chronic urticaria had many other triggering factors and neither was in complete remission after withdrawal of these allergens. IgE sensitization is higher in chronic urticaria patients than in the global adult population, suggesting that it is one important etiopathogenic factor in chronic urticaria. However, it cannot be considered as the expression of an IgE-mediated allergy but as a chronic inflammatory disease, more frequent in IgE sensitized people and favoured by multiple factors, among which IgE-mediated allergy is exceptional.

Key words: chronic urticaria, IgE sensitization, atopy, allergy, adulthood

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Chronic urticaria (CU) is a frequent skin inflammatory disease expressing as either chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CIU), including physical and other inducible CU [1]. IgE sensitization and autoimmunity are etiopathogenic factors involved in chronic urticaria (CU), resulting in activation of mast cells and basophils [2, 3]. Atopic patients produce high levels of IgE that bind to high affinity Fc ϵ RI molecules at the mast cell surface. A subgroup of CU patients synthesizes autoantibodies which interact with IgE and/or Fc ϵ RI. Therefore, in both atopic and autoimmune CU, binding of antibodies to mast cell surface molecules transduces activation signals leading to mast cell activation. Basophils, like mast cells, are activated in CU, as shown by the basal upregulation of CD63 in both atopic and autoimmune CU [4].

The atopic diseases include eczema and/or allergic rhinitis/conjunctivitis/asthma. IgE sensitization is the main biological criterion of atopy and indicates a propensity to develop immunoglobulin E (IgE) antibodies to environmental proteins (i.e. sensitization to allergens). It is defined by the presence of at least one positive skin prick test to environmental allergens and/or high serum levels of allergen specific IgE and/or high serum total IgE levels [5]. However, IgE sensitization is often observed in patients without atopic diseases in whom it is considered to reflect an atopic background [6].

Since the end of the nineteenth century, many authors have considered that CU is one of the atopic diseases [7]. Recent reports even suggested that the vast majority of CU patients are atopic [8]. Moreover, there is still controversy as to whether CU could be the expression of an IgE-mediated allergic reaction following exposure to aero- or food allergens [9, 10]. Although some acute intermittent urticaria indisputably results from IgE-mediated sensitization, allergy has only exceptionally been directly related to chronic urticaria (CU) and always in imprecise reports [11]. However, clinical studies addressing this point are lacking. We report herein a prospective study investigating the IgE sensitization status and the relevance of allergy in 128 adult CU patients. We show that the proportion of CU patients with an IgE sensitization is in the range of that reported for the main atopic diseases. However, we did not find any patient with proven IgE-mediated CU.

Abbreviations:

Abs	antibodies
ANA	antinuclear antibodies
Anti-H1	anti-histaminic 1
CU	chronic urticaria
IDT	intradermal test
NSAID	non steroid anti-inflammatory drug
SPT	skin prick tests
TPO	thyroperoxydas

Table 1. Number of CU patients (and percentages) with positive skin prick tests (SPT) among 105 prick-tested.

Allergen tested	SPT +/105	Percentage %
<i>Aeroallergens</i>		
Dust mites (DF, DP)	18	17
Dog allergens	4	3.8
Cat allergens	4	3.8
German cockroach	5	4.7
Mould	1	0.95
Grass/corn/Plantain	21	20
Weeds (artemisia, ambrosia)	15	14.3
4 trees mix pollens	6	5.7
Latex	3	2.8
<i>Food allergens</i>		
Standard allergens		
Egg (white, yolk)	0	0
Nut	1	0.95
Soya	1	0.95
Celery-turnip	3	2.8
Wheat	0	0
Lupin	0	0
Mustard	0	0
Shrimp	0	0
Brewer's yeast	0	0
Miscellaneous allergens: crab, hake, peas	3	2.8

Patients and methods

Patients

This prospective study was carried out from December 2006 to August 2008. The patients were adults suffering from CU, defined by the existence of wheals and/or facial oedema, several times a week for at least 6 weeks. Intermittent urticaria, with periods without lesions longer than those of flares, was excluded. Patients agreed to a standard check-up during a one day hospitalisation consisting of: i) a standard questionnaire about their personal and family history, triggering or worsening factors and response to previous treatments; ii) a blood serum analysis (blood cell counts, C reactive protein, ASAT, ALAT, antinuclear and antithyroperoxidase antibodies, total IgE level; iii) physical tests including pressure (immediate and delayed responses), heat, cold and exercise; iv) skin prick tests (SPT) with 13 commercially available aeroallergens and 16 food allergens (Stallergenes, Anthony, France) (*table 1*), completed with allergens suspected by the patient. In the case of positivity of a skin test, the clinical history was further investigated to evaluate its relevance for the urticaria. The CU was related to allergy if there was: i) a high correlation between positive SPT and the case history, with a one hour time limit between exposition to the allergen and flares of urticaria ii) complete remission of urticaria during the next two months

after withdrawal of the allergen. Urticaria was considered as severe if unresponsive to or only mildly improved (< 50%) by anti-histaminic (anti-H1) therapy (up to 4 tablets of non-sedative drugs) and if the patient exhibited at least two of the three following criteria: sleep disturbance due to itching, repeated angioedema, general symptoms.

Skin prick tests

Anti-H1 treatment was stopped 5 days before hospitalisation. A skin test was considered as positive if the papule measured at least 3mm or was at least equal to the mean diameter of the positive control, according to international guidelines [12]. Positive (histamine, codeine) and negative (saline) controls were carried out in parallel.

Serum IgE and autoantibodies

Serum IgE was assessed by fluoroenzymimmunoassay Immucap 250 Phadia (N < 150 KU/L).

Antinuclear Abs (ANA) were assessed by indirect Immunofluorescence on Hep 2 cells (N < 100) and antithyroperoxidase (antiTPO) Abs by Radio Immunologic Assay (N < 60 Ku/L).

IgE sensitization- autoimmune background

IgE sensitization to environmental allergens was defined by the positivity of at least one skin prick test and/or elevated levels of serum IgE (≥ 300 Kui/L). Autoimmune status was defined by the presence of circulating antinuclear Abs ≥ 100 and/or antiTPO Abs above 60 kU/L.

Results

Among the 128 patients, aged 15 to 77 years (mean: 40.7; median: 39), 51 were men and 77 were women (sex-ratio 0.39). Forty-eight patients had spontaneous CU (38%), 3 patients had exclusively inducible CU (2%) and 77 patients had both spontaneous and inducible CU (60%). Twenty-four (19%) had an anti-H1-resistant urticaria. The standard questionnaire was fully completed by 110 patients (*table 1*) and 105 had interpretable SPT (*table 2*).

IgE sensitization

Forty/105 patients (38.1%) had at least one positive SPT, 32/105 (30.4%) two or more positive SPT and 49/105 (46.7%) had either one positive SPT or an IgE serum level ≥ 300 Kui/L. Thirty-nine patients had positive SPT for aeroallergens and 6 patients had positive SPT for food allergens (5 patients had positive tests for both food and aeroallergens).

Fifteen/105 patients had anti-H1-resistant urticaria. Nine/15 (anti-H1-resistant) and 31/90 (anti-H1-sensitive) patients had at least one positive SPT ($p=0.08$ not significant).

Table 2. Clinical and laboratory findings of 128 adult patients with chronic urticaria.

Demographic data (n = 128)	
Sex of patients	
Male: 51; female: 77; Sex-ratio: 0.39	
Age of patients (years)	
Mean: 40.7 (+/-14.9)	
Subjective data from the questionnaire (% , n = 110)	
Symptoms ^a	
pruritus: 80	
skin pain: 20	
arthralgiae or myalgiae: 18	
fever or chills: 8	
digestive disturbance: 2.7	
Triggering or worsening factors ^a	
physical: 62 (including delayed pressure urticaria: 2 and cold urticaria: 7)	
stress: 61	
drugs: 20	
food: 13	
infection: 8	
none: 11	
Response to anti-H1 (%):	
excellent (> 70% improvement): 30	
poor (< 20% improvement): 13.5	
intermediate (> 20% et < 70%): 56.5	
Aetiological classification and laboratory abnormalities (% ; n = 128)	
Vasculitis urticaria and rare syndromes: none ^b	
Allergic urticaria: none	
Autoantibody positivity alone (%):	
Antithyroperoxidase + (≥ 60 kU/L): 11.7,	
antinuclear (≥ 100): 25 (TPO + and AN + :4.7, TPO + or AN + : 31.3)	

^a Some patients had several symptoms or factors.

^b One patient had a low rate monoclonal IgM with an excellent response to anti-H1; another patient had a slightly positive Farr test without other arguments for a systemic lupus erythematosus.

Atopy and CU

Personal, familial (first-degree relatives), familial and/or personal histories of atopic diseases were reported by 42%, 55.5%, 68% of the CU patients, respectively, suggesting that atopy is strongly linked to CU.

Allergy and CU

Only one woman claimed that exposure to artemisia pollen (to which she was sensitized) worsened her urticaria and one man had relevant tests for food allergens (flares of urticaria after ingestion of celery or sesame). In fact several factors were inducing urticaria flares in these two patients: psychological stress, NSAIDs and heat. Neither of them had complete remission following avoidance of these allergens. Therefore, no pure or mainly allergic CU was diagnosed in our patients.

Table 3. Number (and percentage) of patients with IgE sensitization** and/or autoimmune status*** among 105 prick-tested patients.

	Autoimmune status +	Autoimmune status -	Total
IgE sensitization +	15 (14.3%)	34 (32.4%)	49 (46.7%)
IgE sensitization -	20 (19%)	36 (34.3%)	56 (53.3%)
Total	35 (33.3%)	70 (66.7%)	105 (100%)

At least one positive prick-test and/or IgE level ≥ 300 KU/L. *ANA positivity ≥ 100 and/or antiTPO Abs ≥ 60 kU/L.

Discussion

CU is not an allergic disease

The important observation in our study is that allergy was not found to be responsible for CU, even if it was one of the triggering factors of urticaria flares in two patients.

The question of the reality of allergic CU is an important concern and has been the topic of several studies, with conflicting results. In a retrospective study of 350 CU patients, Guinpain claimed that 17 CU patients were healed after avoidance of food allergens [13]. This is in sharp contrast to the study of Juhlin [14] who noted that, although 58% of 330 patients presented with food-aggravated CU (and four of them had food-specific serum IgEs), none of them was cured by the withdrawal of the suspected food. Pigatto *et al.* reported 15 double-blind, placebo-controlled oral positive challenges (a majority to peas and peanuts) in a 348 CU population [15], confirming that food-aggravated urticaria flares are common [16]. However, in this study, as in many others, no information was given on the evolution of CU after allergen avoidance [17-19]. Similarly, some reports of positive provocation challenges are debatable for suspected IgE-mediated allergy, as the cut-off time for a positive test was either not defined or was as long as 24 hours, which appears too long for an allergen-IgE-induced urticaria flare [3, 10, 20].

Kaplan, cited by Greaves [21], did not find any relevant food allergy in 1200 CU patients observed between 1995 and 2003. Likewise, Kulkathan reported that one-third of 88 CU patients had SPT to food but only one patient had clinical relevance of food-induced urticaria [22]. Volokanis, on the other hand, reported three convincing cases of pollen-induced CU in childhood, as the disease was active only during the pollen season over at least 2 years [10].

CU, IgE sensitization and atopy

Results of this prospective study show that the prevalence of IgE sensitization (table 3) in CU is 46.7%, a rate which is in the range of that observed in adult rhinitis and/or asthma (44 to 69.3%) [23-25] and above the prevalence of IgE sensitization in the general adult French population [26-28]. The prevalence of IgE sensitization (defined as sensitization to at least one common allergen, diagnosed by SPT or specific IgE) in populations aged 20-44 years varies greatly from one country to another and has been estimated between 16.2 and 44.5% in 22 countries in the European Community Health Survey (ECHRS), with a

28-29% proportion in French centers [26-28]. Prevalence of IgE sensitization was higher (32%) in Poland, Switzerland and Italy [29-31] and occurred in up to 46% of individuals in Turkey and Finland [32, 33].

Our results linking CU and IgE sensitization in nearly 50% of patients are in keeping with previous results [34-36] but do not confirm the most recent study, stating that the vast majority (> 90%) of CU patients are atopic [8]. Using one positive skin prick test to environmental allergens as the indication of atopy, Volonakis and Kulkahan found 31.1% and 47% of IgE sensitization in Greek CU children and Thai CU adults, respectively [10, 22]. However, the real proportion of sensitized patients in these studies is probably underestimated by the use of SPT alone to define IgE sensitization. Indeed, our data show that an additional 8.5% of CU patients were considered sensitized if the elevated serum IgE levels were considered. Of note, hyper IgE above 300 kU/L has an 80-98% predictive positive value for IgE sensitization [37].

CU and autoimmunity

Besides IgE sensitization, autoimmunity has been associated to CU. Autoimmune urticaria defines a subset of patients who produce autoAbs to mast cell surface molecules, including FcεRI. These autoAbs are detected by an intradermal test (IDT) to autologous serum and induce a wheal and flare reaction [38]. Patients with urticaria often exhibit features of autoimmunity since they also produce Abs to a variety of autoantigens including nuclear antigens (ANA) and thyroid antigens (anti-TPO Abs) [39]. Although the aim of the present study was not to precisely analyze autoimmune CU (we did not perform IDT with autologous serum), we checked for an autoimmune status in our patients by testing for the presence of serum ANA and anti-TPO Abs. We observed that 35/105 patients (33%) had an autoimmune status defined by the presence of ANA above 80 and/or anti-TPO Abs above 60 kU/L. Fifteen/35 (43%) autoimmune CU had also IgE sensitization. Finally, 36/105 CU patients (34%) had neither IgE sensitization nor an autoimmune status.

Conclusion

The present study demonstrates that CU is not an allergic disease. IgE-mediated allergy may very rarely be one of the aggravating factors of CU but is almost never sufficient to explain the chronicity of urticaria. We also confirm that up to 50% CU patients exhibit IgE sensitization. Autoimmunity is found in one third of CU patients. ■

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