Original Article

Bronchial hyperresponsiveness is a common feature in patients with chronic urticaria

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Summary. *Background:* Chronic urticaria (CU) is a skin disorder characterized by long-lasting release of histamine, and sometimes leukotrienes, from both mast cells and basophils. Although both these substances are potent inductors of contraction of airway smooth muscle, pulmonary function and airway hyperresponsiveness have not been systematically investigated in patients with CU.
Objective: To assess pulmonary function and airway hyperresponsiveness in patients with CU.
Methods: Twenty-six clinically well-characterized adult patients with CU (M/F 8/18; mean age 47 years) underwent pulmonary function tests and methacholine provocation during a phase of moderate activity of their disease. Twenty-six adult asthmatic patients submitted to methacholine provocation were used as controls.
Results: Two patients (8%) had overt asthma on baseline pulmonary function tests. Twenty (77%) patients with a normal baseline pulmonary function showed significant bronchial hyperresponsiveness on methacholine provocation. Altogether, 22/26 (85%) patients had asthma or abnormal bronchial reactivity. Airway hyperresponsiveness was not associated with gender, disease duration, intolerance to NSAID, positive autologous serum skin test or respiratory allergy. On average, asthmatic controls showed a much severer airway hyperresponsiveness than urticaria patients ($p < 0.01$).
Conclusion: Patients with CU frequently show bronchial hyperresponsiveness. Prospective studies are needed to assess whether they are at risk for bronchial asthma.

Key words: Chronic urticaria, asthma, airway hyperresponsiveness, methacholine, histamine.

Resumen. La urticaria crónica (UC) es una afección cutánea caracterizada por una liberación de larga duración de histamina, y a veces leucotrienos, por parte de mastocitos y basófilos. Aunque estas dos sustancias son potentes inductores de la contracción del músculo liso de las vías respiratorias, todavía no se ha investigado de forma sistemática la función pulmonar y la hiperreactividad bronquial en pacientes con UC.
Objetivo: Evaluar la función pulmonar y la hiperreactividad bronquial en pacientes con UC.
Métodos: Veintiséis pacientes adultos clínicamente bien caracterizados con UC (V/M 8/18; edad media de 47 años) fueron sometidos a pruebas de función pulmonar y provocación con metacolina durante una fase de actividad moderada de su enfermedad. Se utilizó como control a 26 pacientes asmáticos adultos sometidos a provocación con metacolina.
Resultados: Dos pacientes (8%) presentaron asma manifiesta en las pruebas basales de la función pulmonar. Veinte pacientes (77%) con una función pulmonar basal normal mostraron hiperreactividad bronquial significativa tras la provocación con metacolina. En total, 22 de los 26 pacientes (85%) presentaron reactividad bronquial anormal o asma. La hiperreactividad bronquial no se asoció con el sexo, la duración de la enfermedad, la intolerancia a los AINE, la prueba cutánea con suero autólogo positiva ni la alergia respiratoria. De promedio, los controles asmáticos mostraron una hiperreactividad bronquial mucho más grave que los pacientes con urticaria ($p < 0,01$).
Conclusión: Los pacientes con UC presentan hiperreactividad bronquial de forma frecuente. Son necesarios estudios prospectivos para evaluar si presentan riesgo de padecer asma bronquial.

Palabras clave: Urticaria crónica, asma, hiperreactividad bronquial, metacolina, histamina.

Introduction

Chronic urticaria (CU) is a skin disorder characterized by the recurrent eruption of transitory, itchy wheals sometimes associated with angioedema for more than 6 weeks. In recent years, several studies showed that in 30-60% of patients with active disease, the intradermal injection of autologous serum causes a wheal-and-flare reaction [1-5] and that the serum of most of such patients causes histamine release from basophils of healthy subjects [1-9]. Histamine-releasing activity may be induced by IgG autoantibodies directed against the IgE high affinity receptor (FcεRI) [6], against IgE [2,3], or by not yet characterized serum factors [5].

Although histamine released from both mast cells and basophils is the main mediator involved in urticaria, the serum from a subset of patients with CU, particularly those positive on autologous serum skin test, is able to induce *de-novo* production of sulfidoleukotrienes (SLT) in human basophils as well [10]. Both histamine and SLT are potent inductors of contraction of airway smooth muscle [11,12] but surprisingly enough the respiratory function in patients with a disease characterized by chronic and systemic release of these substances has received little attention. The present study aimed to investigate both pulmonary function and bronchial hyperresponsiveness in a group of patients with CU.

Patients and methods

Patients

Forty consecutive patients with CU (defined as the recurrence of hives and/or angioedema for more than 6 weeks) seen at this allergy unit were asked to undergo pulmonary function measurements and methacholine provocation tests as a part of their diagnostic protocol. Twenty-six patients (male/female ratio 8/18; age 18-80 years, mean 47 years) accepted to undergo these investigations and represent the study population. The median disease duration was 44 months (range 2-360 months). All the patients were in a phase of moderate activity of their skin disorder when pulmonary investigations were carried out. Eleven patients (42%) reported unequivocal exacerbations of their skin disease after taking nonsteroidal anti-inflammatory drugs (NSAID); in most cases emergency room recordings confirmed these episodes. Atopic status was ascertained in all cases by SPT with a large panel of commercial extracts of airborne allergens (Allergopharma; Reinbeck, Germany) including pollens (grass, mugwort, ragweed, pellitory, plantain, birch, olive, cypress), house dust mites, molds (*Alternaria, Aspergillus, Cladosporium, Candida, Penicillum, Trichophyton*), and both cat and dog dander; readings were taken at 15 min, and reactions were expressed as mean wheal diameter (adding the longest diameter to the orthogonal diameter and dividing it by 2). A wheal diameter of 3 mm or more was considered positive [13]. Five patients out of 26 (19%) were positive on SPT with airborne allergens and all of them had allergic rhinitis (Table 1). No patient, whether with or without respiratory allergy, reported a history of asthma. Routine laboratory investigations including ESR, blood counts, antinuclear antibodies, electrophoresis, and complement fractions were normal in all cases. Both anti-thyroglobulin and anti-peroxidase autoantibodies were detected in 5 patients.

All patients underwent an intradermal test with 0.05 ml of fresh, sterile autologous serum (autologous serum skin test, ASST); 0.05 ml of saline were intradermally injected as negative control [4]. Readings were taken after both 15 min and 30 min, and only the appearance of an unequivocal wheal-and-flare reaction in the site of serum injection in the absence of any reaction to saline was considered as a positive response. Seventeen (65%) patients showed a positive ASST, 8 were negative, and 1 could not be evaluated due to severe dermographism.

Pulmonary function tests and methacoline challenges

Patients underwent pulmonary function tests and methacholine challenges at several pulmonology units in this geographical area as they were left free to carry out these investigations at the most convenient location near their homes. Bronchial challenge tests were performed only in subjects showing a baseline FEV_1 > 80% of the predicted normal. Nonspecific responsiveness was expressed as the concentration in mg/ml of methacholine causing a 20% fall in FEV_1 (PC_{20}) as determined by interpolation between points on the dose-response curve. Methacholine responsiveness was considered severe, moderate, mild, or normal for PC_{20} values < 0.25, 0.26-2.0, 2.1-8.0, and > 8.0 mg/ml, respectively [14]. No patient was taking ß-agonists or corticosteroids when pulmonary challenge tests were performed. Most patients were taking oral anti-histamine tablets (cetirizine, desloratadine, or ebastine in all cases) to control their skin disorder.

Controls and statistics

Twenty-six (26) asthmatic adult patients of comparable age (M/F 10/16, age 17-59 years) submitted to methacholine challenge were used as positive controls. Methacholine data were compared by non parametric means using the Wilcoxon rank sum test.

Results

Results are summarized in Table 1. Two patients were not submitted to methacholine provocation because their basal FEV_1 level was < 80% of the expected value. Twenty (77%) patients with a normal baseline pulmonary function showed significant bronchial hyperresponsiveness on methacholine provocation. Methacholine responsiveness was severe, moderate, and mild in 1, 11, and 9 cases,

Table 1. Clinical features and airway hyperresponsiveness in patients with CIU.

Patient	Age/Sex	DD (months)	NSAID	ASST	Atopy	Baseline FEV_1	PC_{20} (mg/ml)
1	M/72	48	Yes	Negative	No	Normal	0.5
2	F/39	12	Yes	Positive	No	Normal	0.5
3	M/50	12	Yes	Positive	GR	Normal	1.0
4	F/32	120	Yes	Positive	No	Normal	2.0
5	F/80	3	No	Positive	No	68%	ND
6	F/21	200	Yes	Positive	Cat	Normal	0.2
7	F/53	3	No	Positive	No	Normal	0.5
8	F/26	2	No	Positive	No	Normal	2.62
9	M/52	140	Yes	Negative	No	Normal	2.98
10	M/47	2	No	Positive	No	Normal	Negative
11	F/29	16	No	Positive	No	Normal	8.0
12	F/39	2	Yes	Positive	No	Normal	Negative
13	F/49	12	No	Positive	Mite	Normal	Negative
14	F/69	2	No	Dermogr.	No	Normal	Negative
15	M/23	24	No	Positive	G	74%	ND
16	M/68	24	Yes	Positive	No	Normal	0.5
17	F/69	360	No	Negative	No	Normal	3.9
18	F/44	2	Yes	Negative	Olive	Normal	8.0
19	F/58	4	Yes	Negative	No	Normal	1.0
20	M/47	30	Yes	Negative	No	Normal	0.5
21	F/61	26	No	Negative	No	Normal	4.0
22	M/44	3	No	Negative	No	Normal	4.2
23	F/50	36	No	Positive	No	Normal	4.0
24	F/36	16	No	Positive	No	Normal	1.7
25	F/19	28	No	Positive	No	Normal	3.4
26	F/49	24	No	Positive	No	Normal	2.0

DD: Duration of chronic urticaria (months); NSAID: History of exacerbation by nonsteroidal anti-inflammatory drugs; ASST: Autologous serum skin test; Dermogr: Dermographism; Atopy: G = grass, R = ragweed; ND: Not done.

respectively. Four patients showed a normal bronchial responsiveness. Altogether, 22/26 (85%) patients had overt asthma or abnormal bronchial reactivity. Airway hyperresponsiveness was not associated with gender, disease duration, intolerance to NSAID, positivity on autologous serum skin test or respiratory allergy (Table 1). Not surprisingly, all asthmatic controls showed severe or moderate bronchial hyperresponsiveness; on average this was significantly more severe in asthmatic controls (Table 2) than in urticaria patients ($p< 0.01$; Wilcoxon rank sum test).

Table 2. Clinical features and airway hyperresponsiveness in 26 asthmatic controls.

Control	Age/Sex	PC_{20} (mg/ml)
1	F/58	0.4
2	F/22	0.05
3	F/47	0.1
4	M/34	2.5
5	M/30	0.2
6	F/28	0.1
7	M/25	0.05
8	F/38	2.0
9	M/44	1.6
10	F/42	0.1
11	F/59	0.2
12	F/22	0.2
13	M/32	0.1
14	F/19	0.2
15	F/28	0.02
16	M/50	0.6
17	F/17	0.3
18	M/26	0.05
19	F/17	0.07
20	F/25	0.06
21	M/32	1.8
22	F/27	0.06
23	M/36	0.1
24	F/44	0.7
25	M/35	0.06
26	M/35	0.2

Discussion

Abnormal airway responsiveness is considered a characteristic feature of asthma [15], but mechanisms underlying this disorder are still poorly defined. In different studies the onset of airway hyperresponsiveness has been linked to one or more genes for atopy on chromosome 5q [16], pollution [17], or viruses [18]. However, other works did not confirm these findings and showed that both IgE and bronchial inflammation are not essential for the development of airway hyperresponsiveness [19-22].

Pulmonary function and airway responsiveness in patients with CU have not been extensively investigated so far. In the only study addressing this question so far, 12 patients with CU did not show reactivity on nonspecific

bronchostimulation with methacholine [23]. The results of the present study are completely different in that 85% of the patients with CU were found to have bronchial hyperresponsiveness (BHR) or, in some cases, overt asthma; this proportion largely exceeded the one expected in a normal population (5-20%) [24]. As expected, the prevalence of hypersensitivity to airborne allergens in this series of patients with CU did not exceed that of the general population, and blood eosinophilia was always absent [25]. By comparison with a matched group of asthmatic controls, airway hyperresponsiveness in CU patients was on average much less pronounced and not particularly severe in most cases. The finding of a high prevalence of BHR in CU patients is not particularly surprising in the light of recent studies showing that the immunopathology of CU is that of an eosinophil and basophil cell-mediated hypersensitivity reaction with a TH0 or a mixture of both TH1 and TH2 cytokine profile [26,27]. Activation of basophils and mast cells can lead to the production of leukotrienes [10,26], IL4, IL5 and histamine [26,27]. It is highly probable that in patients with CU bronchial hyperresponsiveness is a consequence of chronic and systemic release of mediators of bronchial inflammation from eosinophils, basophils and mast cells. The clinical histories of these patients and the pathophysiological data suggest that in CU airway hyperresponsiveness is probably an acquired phenomenon. In these patients bronchial hyperresponsiveness did not depend on the duration of the skin disease: some young patients without respiratory allergy and with a disease duration as short as 2 months showed a marked response to methacholine provocation, suggesting that bronchial inflammation is already present in the earliest phases of CU. The fact that clinically evident urticaria probably follows a period of symptomless, increasing activation of basophils and mast cells [28] might explain this finding. Mast cells play a fundamental, though not exclusive, role in asthma inflammation [29]. The patients in this study were examined during a phase of moderate activity of their disease. Longitudinal studies will ascertain whether bronchial hyperresponsiveness persists or decreases during the phases of clinical remission of CU. It is generally accepted that subjects with hay fever without a history of asthma may have a fall greater than 20% in FEV_1 following inhalation of methacholine, although usually at concentrations greater that 10 mg/ml [30]. Five patients in this study group suffered from allergic rhinitis. Although one of them showed overt asthma on baseline pulmonary function tests, and another showed a fall of 20% of FEV_1 at a methacholine dose as low as 0.2 mg/ml, it does not seem that their behavior differed from that of non-atopic urticaria patients.

These findings of the present study suggest that CU patients might be at risk for bronchial asthma. A recent work found that patients with intrinsic asthma are frequently positive on autologous serum skin test, a typical feature of at least one half of chronic urticaria patients; moreover, in some cases respiratory symptoms were associated with chronic urticaria [31]. These findings were confirmed by another study that found a prevalence of 58% of positive autologous serum skin test among non-allergic asthmatics vs 0% in allergic controls [32]. The present study represents a further link between two clinical conditions that have been considered totally distinct hitherto. Prospective studies are needed to assess whether asthma eventuates over time in patients with CU. In this sense patients with CU should be watched for possible respiratory symptoms during routine follow-up visits. The detection of bronchial hyperresponsiveness in patients with CU might also prove relevant for a better understanding of mechanisms underlying this complex pulmonary phenomenon.

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