
Bronchial hyperresponsiveness in patients with cholinergic urticaria

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Background: Cholinergic urticaria is occasionally associated with bronchospasm, even in patients without a history of asthma; the underlying mechanism has not been elucidated.

Objective: To evaluate bronchial hyperresponsiveness (BHR) in patients with cholinergic urticaria compared with healthy adults and patients with chronic urticaria.

Methods: Patients with a history of cholinergic urticaria and a positive ergometric test result constitute the study group. History was reviewed and physical examination and spirometry were performed to exclude exercise-induced anaphylaxis and exercise-induced asthma. Patients with chronic urticaria and healthy volunteers were used as positive and negative controls, respectively. All 3 groups were evaluated for BHR using a methacholine challenge test.

Results: Fifty-nine adults participated in the study: 30 patients with cholinergic urticaria, 15 with chronic urticaria, and 14 healthy volunteers. BHR was demonstrated in 13 of 30 patients (43%) in the study group, 1 of 15 patients with chronic urticaria (7%), and 1 of 14 healthy volunteers (7%); the observed difference was statistically significant. Further analysis of the study group demonstrated the existence of 2 subpopulations of patients with cholinergic urticaria, which were discriminated on the basis of intensity and duration of symptoms, with 96.7% accuracy. In addition, a statistically significant correlation was found between patient age and disease duration and between intensity and frequency of symptoms.

Conclusions: Evaluation of patients with cholinergic urticaria should probably include BHR. A formula based on duration and intensity of cholinergic urticaria symptoms is provided as a tool for the prediction of BHR.

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INTRODUCTION

Physical urticarias constitute a diverse group of chronic urticaria induced by a variety of physical stimuli, such as pressure, rubbing, exercise, cold, heat, sunlight, vibration, and water. Cholinergic urticaria accounts for approximately 30% of all physically induced urticarias¹ and for nearly 7% of all types of chronic urticaria.^{2,3}

Cholinergic urticaria, first described by Duke in 1924,⁴ is triggered by a rise in core body temperature during active (exercise) or passive (high environmental temperature) warming. It is characterized by the appearance of numerous punctate, monomorphic wheals (1–3 mm) surrounded by large flares, initially on the trunk and later on the neck, face, and extremities; however, lesions may appear on any part of the body. They usually begin 5 to 15 minutes after exposure to the triggering stimulus. Occasionally, patients complain of an itching, tingling, or burning sensation before the appearance of urticarial lesions; the skin eruption usually lasts 20 to 30 minutes. Pulmonary and other extracutaneous symptoms have been reported during episodes of cholinergic urticaria^{5–18} that need to be differentiated from exercise-induced anaphylaxis^{16–19} and exercise-induced asthma.²⁰

A search of the literature revealed that bronchial hyperresponsiveness (BHR) has not been investigated as a probable predisposing factor for pulmonary symptoms in patients with cholinergic urticaria. On the basis of this finding, the present study was performed initially to investigate BHR to methacholine in patients with cholinergic urticaria and to compare it with that in patients with chronic urticaria and healthy adults.

METHODS

Outpatients who had visited the allergology clinics of 3 tertiary hospitals (referral centers for central and southern Greece) for evaluation of either cholinergic or chronic urticaria were invited to participate in the study on a volunteer basis. Eighty-four patients were screened, and 45 (30 with cholinergic urticaria and 15 with chronic urticaria) were enrolled. Twenty-nine healthy adults were interviewed from the technical and administrative personnel of the institutions, and 14 were enrolled in the study; thus, a total of 59 individuals participated.

The inclusion criteria consisted of being aged 14 to 60 years,²¹ normal echocardiographic and cardiac evaluation findings, positive ergometer challenge test results for patients with cholinergic urticaria, disease duration of 6 weeks or more, and a history of satisfactory symptom control with histamine₁ antagonists for patients with chronic urticaria.

The exclusion criteria consisted of the following: (1) a history of asthma, other respiratory diseases, or chronic disorders, particularly those mimicking asthma and those requir-

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ing continuous drug ingestion; (2) atopy, defined as a positive skin prick test response to more than 1 of 12 inhalant allergens common in the area (grasses, *Parietaria*, olive, mixed *Cupressaceae*, *Chenopodium*, *Artemisia*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*, *Cladosporium*, cat, and dog); (3) a history consistent with physical urticarias, including symptomatic dermatographism (non-symptomatic dermatographism, usually manifested as persistent erythema without wheal and pruritus, was not considered an exclusion criterion); (4) a smoking history (ex-smokers were also excluded); (5) the inability to perform acceptable-quality spirometry; (6) pregnancy and lactation; (7) respiratory tract infection during the preceding 6 weeks; and (8) exposure to chemical irritants.

Medication use discontinuation before the challenge test was required as follows: (1) 10 and 3 days for antihistamines for the cholinergic urticaria and chronic urticaria groups, respectively; (2) 3 days for antileukotrienes; and (3) 3 weeks for depot corticosteroids and 1 week for regular corticosteroids. The medical history of each participant was reviewed thoroughly, and each participant received a complete physical examination. For patients with cholinergic urticaria, the intensity, duration, and frequency of symptoms were recorded at baseline. The grading system for the intensity of symptoms was based on the evaluation of wheals and affected areas of the body (Table 1).

Protocol Design

To exclude exercise-induced asthma, all patients with cholinergic urticaria were subjected, at the first visit, to an exercise challenge test (bicycle ergometer) according to a previously described protocol.²² The target maximal heart rate is defined by the following formula: $220 - \text{age}$ (in years). The work rate was set to 60% of the target in the first minute, 75% in the second minute, 90% in the third minute, and 100% in the fourth minute. The test ended when the patient had exercised at the target work rate for 6 minutes. Spirometry was performed before exercise and also 1, 5, 10, 15, 20, and 30 minutes after exercise. In the event of a patient not developing urticaria within 10 minutes, the exercise test was repeated for a longer duration (15 minutes) 72 hours later^{3,23}; spirometry was also repeated then. The environmental temperature was kept constant at 28°C to 30°C (82°F–86°F) in the challenge laboratory.⁵

Criteria for Diagnosing BHR

On a subsequent visit, both patient groups and the healthy controls underwent a bronchial methacholine challenge test²²

performed in a stepwise manner by doubling the methacholine concentration from 0.0039 to 2.00 mg (cumulative dose). Spirometry was performed 1 minute after each inhalation. A decrease of 20% or more in FEV₁ was considered to be a positive result, and the test was terminated at that point. Results of the BHR test were considered positive if the provocation dose that caused a decrease in FEV₁ of 20% (PD₂₀) was less than 2 mg.²⁴ The magnitude of BHR was expressed as the level of PD₂₀.

Statistical Analyses

The statistical significance of differences in BHR prevalence was evaluated using the Fisher exact test.²⁵ Group means for age, intensity, duration, and frequency were compared using the *t* test.²⁶ A stepwise discriminant analysis was performed to investigate whether the variables (1) patient age, (2) intensity of symptoms, (3) duration of symptoms, and (4) frequency of symptoms could be used to classify cholinergic patients into “BHR” or “non-BHR” groups.^{26,27} Assuming that each patient’s BHR diagnosis is the “gold standard,” the analytical procedure uses the 4 baseline variables to determine multipliers (coefficients) for calculating a composite score that is a linear function of 1 or more of the 4 baseline variables. The composite score can be used in the absence of the BHR diagnostic test to classify a patient into the BHR or non-BHR group.

RESULTS

No patient from the cholinergic urticaria group developed exercise-induced asthma or exercise-induced anaphylaxis during the exercise challenge test, and in 5 patients, the test was repeated for 15 minutes 72 hours later to confirm the diagnosis of cholinergic urticaria. Table 2 provides the results of the methacholine challenge in the 3 study groups. The prevalence of BHR was 43% in the cholinergic urticaria group compared with 7% in the chronic urticaria group and 7% in healthy adults ($P = .02$ for both by Fisher exact test). In the cholinergic patients, the BHR prevalence was not significantly different for males and females ($P > .99$). The 2 control groups showed no statistically significant difference in BHR, whereas the cholinergic urticaria group exhibited a statistically significant difference ($P < .01$ by χ^2 test) compared with both control groups.

Table 3 provides the age and sex of the participants, the described symptoms, the cholinergic urticaria symptom characteristics (intensity, duration, and frequency), and the baseline FEV₁ and PD₂₀ of each participant. The discriminant score and classification for each patient with cholinergic

Table 1. Cholinergic Urticaria Intensity Grading System

Intensity grade	Wheals	Localization
Mild	Isolated punctate lesions	Trunk, neck
Moderate	Punctate lesions + plaques (<5)	Any part of the body except face
Severe	Punctate lesions + plaques (≥5)	Generalized, including face

Table 2. Prevalence of Bronchial Hyperresponsiveness (BHR)

Group	No. of patients	BHR prevalence, No. (%)
Cholinergic urticaria patients		
Males	12	5 (42)
Females	18	8 (44)
Subtotal	30	13 (43)
Chronic urticaria patients		
Males	7	0
Females	8	1 (13)
Subtotal	15	1 (7)
Healthy adults		
Males	6	0
Females	8	1 (13)
Subtotal	14	1 (7)

urticaria is shown in the last column of Table 3. "Described symptoms" cannot be used in the analysis as an independent variable because it is highly related to BHR. Therefore, the analysis variables are patient age and symptom characteristics of cholinergic urticaria. The means for age, intensity, duration, and frequency were each significantly higher in patients with cholinergic urticaria and BHR compared with those without diagnosed BHR (Table 4).

The results of stepwise discriminant analysis are depicted in Figure 1. The analysis revealed that symptom duration and intensity are the significant variables in the discrimination. Each patient is classified into 1 of the 2 subgroups, according to whether the discriminant score of the patient is above or below the discriminant limit (d), which is provided by the following formula:

$$d = 1.428 * \text{intensity} + 0.108 * \text{duration} - 4.520$$

(a d value >0 indicates BHR, otherwise a non-BHR case).

The stepwise discriminant analysis also revealed that (1) on resubstituting the intensity and duration scores for each patient with cholinergic urticaria into the discriminant function to obtain composite scores, all 17 patients who did not have confirmed BHR were correctly classified (specificity, 100%), and 12 of 13 with confirmed BHR were correctly classified (sensitivity, 92.3%); overall, 29 of 30 patients (96.7%) were correctly classified (Table 5); (2) the coefficients for duration and intensity, through standardization, become 0.830 and 0.825, respectively, suggesting an equal contribution; and (3) the average values of intensity (2.54) and duration (21.23) in the BHR cases were significantly higher than the corresponding values in the non-BHR group (1.58 and 8.41, respectively). The values of the other 2 variables (age and frequency) were also higher but did not reach statistical significance.

DISCUSSION

Cholinergic urticaria is a physical type of cutaneous allergy; several hypotheses have been proposed regarding its patho-

genesis, but the underlying mechanism has not been clarified. This eruption occurs after sweating, yet cholinergic urticaria also appears in patients with hypohidrosis; ductal occlusion at the superficial acrosyringium and subsequent leakage of inflammatory sweat materials have been proposed as an explanation in this select group of patients.^{28,29} An elevated number of muscarinic receptors in areas with hives has been demonstrated.³⁰ Serum samples from 7 of 16 patients with cholinergic urticaria (44%) gave a positive transfer test result to the skin of a primate.³¹ The application of a tourniquet proximal to a site of increased heat exposure has been shown to eliminate the wheal response⁵; the involvement of a neurogenic reflex is, therefore, suggested. The reduction of α_1 -antichymotrypsin mediator, which may inhibit a protease-causing mast cell activation, is possibly important in the pathogenesis.⁸ Hypersensitivity responses (type I) to autologous sweat^{32,33} have been reported and are supported by positive intradermal test results. Acetylcholine is believed to play a significant role in the development of cholinergic urticaria symptoms.^{3,8,10,19} Increased sympathetic activity stimulates eccrine sweat glands through the action of acetylcholine. It has been proposed that acetylcholine also leads to mast cell degranulation and the release of various mediators, which are responsible for the urticarial response.¹⁸ The intradermal injection of 100 methacholine units elicits a positive reaction in one-third of patients with cholinergic urticaria.³

Cholinergic urticaria is often associated with pulmonary symptoms (chest tightness, wheezing, and dyspnea) and less frequently with other extracutaneous manifestations, yet the exact changes in respiratory physiologic factors have not been studied in depth.⁹⁻¹³ Notable exceptions to this statement are the studies by Soter et al⁶ and Czarnetzki et al,⁷ who evaluated lung mechanics in cohorts of 7 and 21 patients with cholinergic urticaria, respectively. However, these 2 studies may have overestimated pulmonary involvement in cholinergic urticaria because the patient sample studied by the first group of investigators was small and included individuals who reported respiratory symptoms by a factor of 6 to 1. Also, in the study by Czarnetzki et al, patients with cholinergic urticaria and allergic diseases were not excluded. Exercise-induced asthma was not evaluated in either study.

The main objective of this study was to investigate BHR as a potential feature in cholinergic urticaria predisposing such patients to bronchospastic responses during urticarial episodes. These results showed a significantly increased incidence of BHR (43%) in patients with cholinergic urticaria compared with those with chronic urticaria and healthy adults (7% and 7%).

The low occurrence of BHR in the 2 control groups (healthy adults and patients with chronic urticaria) is probably due to the exclusion of asthmatic patients, smokers, and patients with atopy, who exhibit an increased frequency of BHR³⁴; previous screening of unselected general population from our area (K.P., K.K.-F., C.G., unpublished data, 2008) has shown close to twice as high BHR.

Table 3. Variables of Cholinergic Urticaria Related to BHR

Patient No./ sex/age, y	Cholinergic urticaria symptoms			Baseline FEV ₁ (%)	BHR (PD ₂₀), mg	Described symptoms	Discriminant scores
	Intensity ^a	Duration, mo	Frequency ^b				
1/F/53	2	24	2	2.27 (96)	0.525	S, R	0.93 ^c
2/M/20	2	12	1	4.24 (99)	...	S	-0.37
3/F/30	3	18	2	3.07 (109)	0.707	S, R	1.71 ^c
4/M/16	3	2	2	4.40 (101)	...	S	-0.02
5/F/25	2	36	1	3.33 (95)	0.693	S, R	2.22 ^c
6/F/36	1	6	1	2.84 (94)	...	S	-2.44
7/F/42	2	12	1	2.37 (102)	...	S	-0.37
8/M/40	3	18	2	3.83 (91)	0.922	S, R	1.71 ^c
9/F/33	2	5	2	3.27 (99)	...	S	-1.12
10/M/41	3	10	3	2.76 (91)	1.097	S	0.84 ^c
11/F/25	1	8	1	3.53 (108)	...	S	-2.23
12/M/19	2	3	1	4.76 (108)	...	S	-1.34
13/F/45	3	24	3	2.24 (99)	0.04	S, R	2.36 ^c
14/M/25	2	8	3	4.34 (94)	0.134	S, R	-0.80 ^d
15/F/33	1	24	2	2.96 (103)	...	S	-0.50
16/M/28	2	12	1	4.01 (92)	...	S	-0.37
17/F/15	3	6	2	2.65 (92)	0 (NS)	S, R	0.41 ^c
18/F/22	2	5	1	3.94 (114)	...	S	-1.12
19/F/43	3	30	2	2.83 (93)	0.672	S	3.00 ^c
20/M/20	2	18	1	5.00 (108)	0.542	S	0.28 ^c
21/M/19	1	6	1	5.19 (108)	...	S	-2.44
22/F/17	2	4	2	3.16 (99)	...	S, R	-1.23
23/M/24	2	24	2	4.87 (102)	0.095	S, R	0.93 ^c
24/F/14	1	3	1	3.05 (103)	...	S	-2.77
25/M/26	1	18	1	4.26 (99)	...	S	-1.15
26/F/46	2	36	3	2.24 (99)	0.067	S, R	2.22 ^c
27/F/42	3	24	2	3.43 (101)	0.466	S	2.36 ^c
28/M/39	2	12	2	4.25 (101)	...	S, R	-0.37
29/F/22	1	6	1	3.58 (108)	...	S	-2.44
30/F/22	1	5	2	3.51 (111)	...	S	-2.55

Abbreviations: BHR, bronchial hyperresponsiveness; FEV₁, forced expiratory volume in 1 second; NS, normal saline (administered after baseline spirometry and before the first dose of methacholine); PD₂₀, provocation dose that caused a decrease in FEV₁ of 20%; R, respiratory (chest tightness or pressure, cough, and dyspnea); S, skin.

^a Severe = 3, moderate = 2, and mild = 1.

^b Every day = 3, order of week = 2, order of month = 1, rarely = 0.

^c BHR according to the magnitude of the discriminant score.

^d Misclassified.

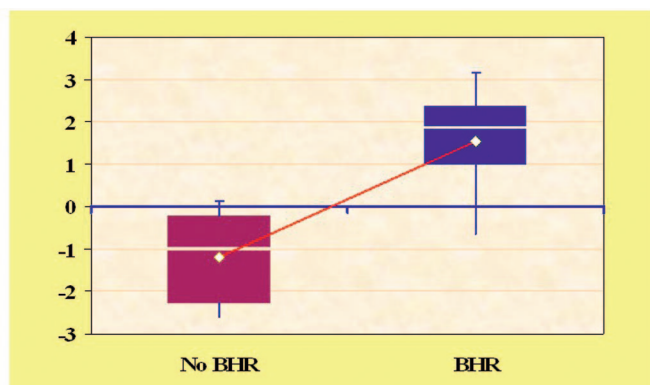
Table 4. Characteristics of Patients With Cholinergic Urticaria by BHR Status

Characteristics	Diagnosed BHR (n = 13)	No Diagnosed BHR (n = 17)	P value
Age, mean (SD), y	34.5 (11.9)	25.5 (8.4)	.02
Intensity, mean (SD)	2.5 (0.5)	1.6 (0.6)	<.001
Duration, mean (SD), mo	21.2 (9.6)	8.4 (5.9)	<.001
Frequency, mean (SD)	2.2 (0.7)	1.4 (0.5)	<.001

Abbreviation: BHR, bronchial hyperresponsiveness.

The previous findings seem to be of importance and question the role of circulating histamine, which has been proposed by some investigators to be the culprit of systemic cholinergic urticaria manifestations, including broncho-

spasm.^{5,6,35} Elevated levels of histamine have, indeed, been detected in serum during acute episodes of cholinergic urticaria^{6,8,36,37} as a result of increased releasability. However, increased releasability has also been observed in chronic urticaria³⁸ without any pulmonary symptoms. Other mediators of the allergic reaction—preformed or de novo synthesized—might lead to BHR. Different combinations of such mediators have been detected in the various subtypes of urticaria and do not necessarily lead to bronchial symptoms.³ Primary neurogenic abnormalities, such as β -adrenergic blockade, increased α -adrenergic responsiveness, cholinergic overreactivity, and defects in the nonadrenergic noncholinergic inhibitory system, should be considered as potential causes of BHR.³⁹ It is well established that the autonomic nervous system is important in regulating airway smooth muscle tone, and, therefore, responses to stimuli such as



	Count	Min	1 st Quartile	Median	3 rd Quartile	Max	Mean	SD
Non BHR	17	-2,61	-2,29	-0,99	-0,21	0,14	-1,19	0,95
BHR	13	-0,64	1,00	1,86	2,37	3,15	1,55	1,07

Figure 1. Box and whisker plot of the discriminant scores. The horizontal line in the middle of each box indicate the median, and the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box mark the 90th and 10th percentiles. In the matrix, the corresponding values of the discriminant scores of the 2 subgroups are compared for 0% (minimal), 25% (1st quartile), 50% (median), 75% (3rd quartile), and 100% (maximal [max]) values. BHR indicates bronchial hyperresponsiveness; and min, minimum.

Table 5. Specificity and Sensitivity of Discriminant Classification

Clinical BHR	Discriminant BHR		
	No	Yes	Total
No, No.	17	0	17
Specificity, %	100	0	
Yes, No.	1	12	13
Sensitivity, %	7.7	92.3	

Abbreviation: BHR, bronchial hyperresponsiveness.

exercise, stress, and heat might represent a pathophysiologic link between cholinergic urticaria and BHR. In addition, defects in end-organ reactivity to cholinergic stimuli (eg, signal transduction) should also be considered.

The present findings suggest that patients with cholinergic urticaria demonstrate pulmonary symptoms because of BHR. It would be of interest to have a long-term follow-up of BHR-positive patients with cholinergic urticaria to evaluate the natural course of the disorder and especially the response to known aggravating factors, such as nonspecific irritants, infections, and pollutants. The results of this study, if confirmed by other investigators and in different population groups, might link BHR to the pathogenesis of the disease.

Age, sex, the described symptoms (cutaneous and respiratory), and the generic characteristics of cholinergic urticaria, namely, intensity, duration, and frequency of occurrence, were taken into consideration in the statistical analysis. These symptom characteristics of cholinergic urticaria were chosen because (1) they are easily derived by simple questioning and

(2) there is a lack of objective indices that could be used in the statistical analysis as potential variables affecting the occurrence of BHR. There were consistent differences in the pattern of values expressed in standardized forms in the 2 subgroups (with and without BHR), thus supporting the analysis approach. Patient age can be considered as a proxy compound measure of intrinsic variables, representing various aspects of each unique individual's physical and mental conditions, "body training," "stress," etc, and, therefore, contributing as a random factor.

Stepwise discriminant analysis determined that once intensity and duration entered the classification equation, neither age nor frequency provided additional significant discrimination and neither was not allowed to enter. Classification accuracy was extremely high (96.7%), a finding that might allow use of the derived discrimination formula (*d*) by a physician in practice, as a prognostic tool predicting BHR in patients with cholinergic urticaria. It is also of interest that the average values of intensity and duration in the case of BHR were shown to be significantly higher in the BHR group, whereas the corresponding values for age and symptom frequency were not significant.

In conclusion, cholinergic urticaria, a distinct subgroup of physical allergy that should be differentiated from exercise-induced asthma and exercise-induced anaphylaxis, exhibits BHR in a significant proportion compared with patients with chronic urticaria and healthy controls; BHR seems to depend on qualitative characteristics of cholinergic urticaria (duration and intensity). Additional studies are required to confirm that affected individuals have cholinergic hyperresponsiveness, as suggested by the increased prevalence of positive bronchial methacholine challenge test results.

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