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Evaluation of methacholine challenge test results in patients with chronic unexplained cough

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Abstract

Introduction: Asthma is one of the most common chronic diseases in adults characterized by variable airway obstruction. Asthma is diagnosed with wheezing and shortness of breath, however it sometimes manifests as a chronic cough that is difficult to diagnose and requires spirometry stimulation tests.
Objectives: This study aimed to investigate the relationship between methacholine test results and respiratory symptoms in patients with chronic unexplained cough.
Patients and Methods: In this cross-sectional study, 102 patients with chronic cough and normal basal spirometry were included. All patients underwent a methacholine challenge test, and their airway irritabilities were assessed. Then, the relationship between methacholine test results and clinical symptoms and also demographic characteristics were investigated.
Results: Of 102 patients, 69 (67.6 %) and 33 (32.4%) were female and male, respectively. Most of patients were non-smoker (90.2%). Around 25 (24.5%) patients had a positive methacholine test. Rhinitis had a statistically significant difference between patients with positive and negative tests (positive test group: 48%, negative test group: 23.4%; $P = 0.01$). Postnasal discharge was reported in 60% of positive methacholine test patients, which was significant compared to the negative group (36.4%; $P = 0.03$). Most patients who had positive tests were housewives (76%). Logistic regression showed that female gender (OR: 7.75, 95% CI: 1.7-35.2), postnasal discharge (OR: 3.19, 95% CI: 1.25-8.2), rhinitis (OR: 3.02, 95% CI: 1.17-7.79), and allergy symptoms OR: 3.51, 95% CI: 1.35-9.18) were directly associated with a positive methacholine test.
Conclusion: The presence of airway hypersensitivity, postnasal discharge, allergic rhinitis, female gender and the housewife's job were strongly associated with a positive methacholine test.

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Introduction

Cough is a physiological defense mechanism for clearing the airways of secretions or foreign objects. The mechanisms of cough are well-known and consist of complex afferent, central, and efferent neural pathways (1,2). Cough, especially chronic cough, is one of the most common symptoms that require medical attention (3). A cough lasting for three to eight weeks is considered subacute, and longer than eight weeks is considered chronic. Subacute and chronic cough often occurs due to causes such as sinusitis and asthma (4). Chronic cough is one of the most common complaints of patients referring to physicians. Due to throat irritation and airway hypersensitivity, chronic cough is seen in 5% to 10% of people, especially in women over 50 years of age (5).

Asthma is a syndrome characterized by variable airway obstruction and is considered one of the most common chronic diseases among adults. People with asthma experience some forms of inflammation in the airways that lead to reversible airway obstruction, decreased airflow, and symptomatic shortness of breath in these patients (6). Asthma is one of the most common chronic diseases with increasing prevalence, morbidity, and mortality (7,8). Airway obstruction's clinical signs and location vary in asthma phenotypes (9). Disorders in the pathophysiology of asthma affect the entire tracheobronchial tree and small airways (10,11).

Asthma sometimes manifests itself as a chronic cough called cough-variant asthma (CVA), and in several cases, it is difficult to be diagnosed. Studies show that about 25% to

Key point

In a cross-sectional study, 102 patients with chronic cough and normal basal spirometry, we found, the presence of irritability, pharyngeal secretions, allergies or rhinitis, female gender and housewife's job were strongly associated with a positive methacholine test.

30% of these patients experience the signs and symptoms of classic asthma over time (12,13). According to studies, CVA seems to be one of the most important causes of chronic cough worldwide. In a study by Fujimori et al, the prevalence of CVA was reported to be 56% (14), and in another study by Orejas García et al, its prevalence was reported to be 32% (15).

Spirometric criteria are required to diagnose asthma and clinical symptoms such as wheezing, shortness of breath, chronic cough, or coughing in the cold air or after exercise. These criteria include an increase of 12% or 200 mL in forced expiratory volume (FEV1) or force vital capacity following inhalation of two puffs of beta-adrenergic agonists (16,17). However, in some patients, along with the clinical symptoms of asthma, no spirometry criterion existed for diagnosis. These patients suffer from a set of chronic clinical symptoms without receiving an appropriate diagnosis or treatment (18). A stimulus test is necessary to detect reversible airway obstruction in such cases. Histamine, methacholine, cold-exposed hyperventilation, or physical activity can be used for performing these tests (19,20). Among these tests, methacholine is the best way to diagnose asthma if spirometry is normal. Methacholine as an airway contractor is a parasympathetic analog and a synthetic derivative of acetylcholine's neurotransmitter. Compared to acetylcholine, it is hydrolyzed more slowly by acetylcholinesterase. Due to its resistance to nonspecific cholinesterase, methacholine's effect is longer but can be reduced or eliminated with atropine or other similar anticholinergics (21). The negative predictive value of the methacholine test is above 90%, while its positive predictive value is less than one at a concentration of 90% and is about 70% at a concentration (22).

Thus, definite studies that clarify the relationship between methacholine test results and suspected asthmatic respiratory symptoms have not been conducted among Iranian population yet.

Objectives

The present study was designed and performed to evaluate the results of methacholine test in patients with suspected respiratory symptoms of asthma. Since the methacholine test is not available in all regions of the country, the results of this study can help choose the correct selection of patients to perform the test and treat.

Patients and Methods

Study design

This cross-sectional study was conducted in the spirometry ward of Urmia Imam Khomeini hospital. The study population was all patients with a chronic unexplained cough who were normal in clinical examination and had normal chest and sinus X-rays, and also had normal spirometry. Exclusion criteria were patients with known pulmonary diseases such as asthma, pneumonia, recent respiratory infections, chronic bronchitis, chronic sinusitis. Accordingly, patients with partial or absolute contraindications to methacholine challenge test including FEV1 less than 60 or less than 1 L, pregnant patients, lactating mothers, patients with a history of heart attack or stroke in the last three months, patients with uncontrolled blood pressure BP >200/100 mm Hg, patients taking cholinesterase inhibitors (myasthenia gravis), and patients with known aortic aneurysms were excluded from the study.

The patients were first clinically examined. After ensuring the normal examination and chest X-ray and explaining the test method, the methacholine challenge test was conducted. The challenge was performed according to American Thoracic Society (ATS) guidelines in which continuous breathing for 10 minutes at ten concentrations of methacholine was administered. First, basic spirometry was conducted, and if more than 80% of the expected value was performed, re-spirometry was achieved with normal saline control solution and then methacholine diluent solution, which was benzyl alcohol in our method. After performing the above-mentioned steps, if the FEV1 was less than 20%, the test entered the next stage and continuous two-minute breathing was performed with doubling concentrations. Two minutes after inhalation of each concentration, the patient underwent spirometry, and the test was stopped if each of the FEV1 stages decreased by more than 20%. If the decline in FEV1 is more than 20%, the test should be stopped. If the decreased value in FEV1 was less than 20%, the test was stopped after inhalation concentration of 16 mg/mL and spirometry was conducted, since the patient's vital signs were recorded. The provocative concentration of methacholine causing a 20% drop in FEV1 from baseline is known as the PC20 (provocative concentration-20). PC20 less than 16, less than four, and more than 16 were considered positive, strong, and negative, respectively.

A checklist was completed for each patient, including demographic characteristics (age, gender, occupation, and smoking), duration of symptoms, and type of clinical signs (cough, shortness of breath and wheezing). The necessary treatments were made in case of any complications during the test. If the patient had shortness of breath, wheezing, or decreased oxygen saturation following inhalation of methacholine, the test was stopped immediately. Salbutamol and oxygen inhalation sprays, and if necessary, hydrocortisone injection was used and the patient was excluded from the study.

Statistical analysis

The continuous variables were presented as mean (range) and categorical variables as number (percent). Independent *t* test and chi-square tests were used to compare means and frequencies between patients with and without the methacholine test. A multivariate logistic regression test was used to evaluate the related variables on having a positive methacholine test. The data were analyzed using

SPSS software version 17 and *P* values less than 0.05 were considered a significant level.

Results

In this study, 102 patients were included. Seventy-seven patients (75.5%) and 25 (24.5%) had negative and positive methacholine tests, respectively. Most of the patients were housewives (48%). Thirty-three patients (32.4%) were male, and 69 (67.6%) were female, 92 (90.2%) were non-smokers, and 10 (9.8%) were smokers. Eighty patients (78.4%) had shortness of breath, while 22 patients (21.6%) did not have this complication. Airway hypersensitivity was present in 100 patients (98%). Postnasal discharge was observed in 43 patients (42.2%). The frequency of allergy symptoms was positive in 27.5% of patients, and 74 patients (72.5%) had no allergy symptoms.

The results showed that among patients with a positive methacholine test, two (8%) were male and 23 (92%) were female, and this difference had statistically significant difference ($P=0.003$). Hypersensitivity was reported in all subjects with a positive methacholine test (n=25), while its frequency was 97.4% among subjects with a negative methacholine test (Table 1).

The mean duration of symptoms in patients with a positive methacholine test was 28.9 (1-84) months and was 36.9 (1-360) months among subjects with the negative test, while this difference was not statistically significant ($P=0.53$). The mean age of the subjects with a positive test was 35.08 (19-58) years, and in subjects with a negative test was 35.54 (11-58) years, which was not statistically significant ($P=0.87$; Table 2).

The logistic regression analysis was shown in Table 3. Results showed that all of the variables (except age) were associated directly with having a positive methacholine test and this relationship was statistically significant for the female gender, rhinitis, postnasal discharge, and allergy symptoms. The odd ratio (OR) of having a positive methacholine test was 7.75 times higher in females than in men ($P=0.008$). Postnasal discharge increases the risk of a positive methacholine test (OR=3.19, 95% CI: 1.25-8.2, $P=0.01$). The ORs of rhinitis and allergy symptoms were 3.02 and 3.51, respectively ($P<0.05$).

Discussion

In this research, 33 men and 69 women with chronic unexplained cough were studied. Of 102 patients, 25 (24.5%) patients had positive methacholine test (8% male and 92% female). The parts are related to results should not mention in the discussion section. According to this study, it may be said that the female gender can be considered a

Table 1. Frequency and percentage of risk factors in patients with chronic unexplained cough

Variables		Number	Percent	Methacholine test, No. (%)		*P* value
				Negative	Positive	
Gender	Male	33	32.4	31 (40.3)	2 (8)	0.003
	Female	69	67.6	46 (59.7)	23 (92)	
Smoking	No	92	90.2	71 (92.2)	21 (84)	0.23
	Yes	10	9.8	6 (7.8)	4 (16)	
Job	Student	22	21.6	18 (23.4)	4 (16)	0.009
	Housewife	49	48	30 (39)	19 (76)	
	Employee	22	21.65	20 (26)	2 (8)	
	Others	9	8.8	9 (11.7)	0	
Dyspnea (shortness of breath)	-	22	21.6	18 (23.4)	4 (16)	0.43
	+	80	78.4	59 (76.6)	21 (84)	
Hypersensitivity	-	2	2	2 (2.6)	0	0.41
	+	100	98	75 (97.4)	25 (100)	
History of other diseases	-	83	81.4	64 (83.1)	19 (76)	0.42
	+	19	18.4	13 (16.9)	6 (24)	
Taking other medications	-	81	79.8	64 (83.1)	17 (68)	0.1
	+	21	20.16	13 (16.9)	8 (32)	
Taking anti-hypertensive drugs	-	96	94.1	73 (94.8)	23 (92)	0.6
	+	6	5.9	4 (5.2)	2 (8)	
Reflux	-	79	77.5	58 (75.3)	21 (84)	0.36
	+	23	22.5	19 (24.7)	4 (16)	
Postnasal discharge	-	59	57.8	49 (63.6)	10 (40)	0.03
	+	43	42.2	23 (36.4)	15 (60)	
Rhinitis	-	72	70.6	59 (76.6)	13 (52)	0.01
	+	30	29.4	18 (23.4)	12 (48)	
Allergy symptoms	-	74	72.5	61 (79.2)	13 (52)	0.008
	+	28	27.5	16 (20.8)	12 (48)	

Table 2. Comparison of mean age and duration of symptoms among individuals with positive or negative methacholine test

Variables	Methacholine test: mean (range)		*P* value
	Positive	Negative	
Duration of symptoms (months)	28.96 (1-84)	36.93 (1-360)	0.53[a]
Age (years)	35.08 (19-58)	35.54 (11-58)	0.87[b]

[a] Analysis was performed using the Mann-Whitney U test.
[b] Analysis was performed using Independent *t* test.

Table 3. The odds ratio (OR) and confidence interval for having a positive methacholine test

Variables	OR	95% CI for OR	β	*P* value
Age (y)	0.98	0.1-0.99	0.003	0.87
Gender	7.75	1.7-35.2	2.04	0.008
Smoking	2.25	0. 58-8.74	0.81	0.24
Dyspnea	1.60	0.49-5.28	0.47	0.43
History of other diseases	1.55	0.52-4.64	0.44	0.42
Taking medications	2.31	0.83-6.5	0.84	0.11
Taking anti-hypertensive drugs	1.58	0.27-9.23	0.46	0.60
Postnasal discharge	3.19	1.25-8.2	2.4	0.01
Rhinitis	3.02	1.17-7.79	1.10	0.02
Allergy symptoms	3.51	1.35-9.18	1.25	0.01

risk factor for a positive methacholine test. Although most of the patients were women in this study, women are more sensitive to their symptoms and illnesses and immediately referred to the doctor. Therefore, there is a need to further studies. This is not suitable to the discussion section and should be written in conclusion. Accordingly, a study done by Hara et al showed the relationship between methacholine test results and gender, with no difference between the genders (23).

Rhinitis was also reported as a cough symptom in 48% of people with a positive test, which was also statistically significant. This symptom should also be considered a warning sign of the presence of underlying asthma in patients. Since asthma is associated with atopy, this result was to be expected no need to this sentence. In this study, allergies were reported in 48% of people with a positive test, which was statistically significant, not suitable to discussion section and the presence of allergies was identified as a risk factor for positive methacholine test in people with chronic cough. Furthermore, airway hypersensitivity was reported in 100% of people who tested positive for methacholine, but it was also commonly seen in those who tested negative (97.46%). In the present study, the prevalence of airway irritability was high among the patients; it cannot be considered a risk factor and predictor of asthma

In a study conducted in Tehran, among the clinical symptoms associated with a positive methacholine test, only wheezing was significantly associated with the positivity of the methacholine test. In a study conducted by Woo et al, shortness of breath and wheezing were also positively correlated with methacholine reactivity, whereas cough was inversely related to it. There was a high correlation between the positive methacholine test and the patient's atopic status (24).

Furthermore, 60% of patients who tested positive for methacholine reported post-nasal discharge (PND), which was significant compared to the negative group (36.4%; $P=0.03$). Therefore, PND can be considered one of the predictive signs of asthma; however, it can be an independent diagnosis or a sign of sinusitis. However, further studies are needed to prove its association with asthma. The study conducted by Jung et al displayed that the methacholine test was positive in patients with mild to moderate sore throat secretions, PC20 at 8 to 25 mg/mL, and pharyngeal discharge was identified as one of the most common causes of chronic cough. However, the methacholine test in this study had a 100% diagnostic value for asthma when a 20% drop in FEV1 occurred with a methacholine concentration of less than 8 mg/mL (25).

Most of the patients who tested positive were housewives (76%). This can be due to excessive contact with household mites or allergenic foods during cooking; however, more studies are needed to prove the cause.

Furthermore as the results of this study presented, in people who recently had respiratory symptoms, the methacholine test was more likely to be positive than those who had been symptomatic for a long time. Although this difference was not statistically significant. We hypothesized that the presence of more severe symptoms may have led patients to refer to the doctor sooner. According to the results of this study, smoking was not recognized as a risk factor for asthma. Although smokers were 2.25 times more likely to test positive than non-smokers, it was not statistically significant. In another study, Lee et al showed no significant association between smoking and positive methacholine test (26).

Conclusion

In conclusion, the presence of irritability, pharyngeal secretions, allergies or rhinitis, female gender, and being a housewife were strongly associated with a positive methacholine test and were identified as risk factors for asthma. Therefore, it is recommended that the illness of people who present with symptoms such as cough, irritability, allergies, rhinitis, postnasal discharge should be taken seriously, and symptomatic treatment should be avoided. A complete examination and a methacholine test should be conducted on patients for the possibility of underlying asthma. If the patients are female or housewives, this attention should be doubled, and they should be followed until the final diagnosis of the disease is confirmed. Although smoking was not identified as a risk factor for asthma in our study, it increased the

likelihood of testing positive. Hence smoking cessation is recommended to all patients with asthma or respiratory symptoms.

Limitations of the study

The limitation of the present study was a relatively small sample size of patients and subsequently a low number of patients that were categorized according to chronic unexplained cough. The mentioned limitation may have reduced the power of statistical tests to detect the differences.

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Authors' contribution

MR, MRP, and MSH were the principal investigators of the study. MR, MRP, and MSH were included in preparing the concept and design. MSH collected data and wrote the article draft. MR, MRP revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the manuscript.

Conflicts of interest

The authors declare there is no conflict of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Urmia University of Medical Sciences approved this study (IR.UMSU.REC.1397.232). Accordingly, written informed consent was taken from all participants before any intervention. Moreover, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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