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Pulmonary Function and Methacholine Challenge Tests in Patients with Ulcerative Colitis

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Background: Ulcerative colitis is an inflammatory chronic disease which is believed to be a multi organ condition. The prevalence of ulcerative colitis is reportedly increasing in Iran presenting with the same clinical characteristics as in developing countries. Pulmonary manifestations of ulcerative colitis are increasingly reported. In this study, we investigated the incidence of bronchial hyper-responsiveness (BHR) in ulcerative colitis (UC) patients.

Materials and Methods: Fifty-one UC patients with definite diagnosis referred to Shariati Hospital, Tehran, Iran, were selected to be evaluated with methacholine challenge test from October 2010 to October 2011. Patients were compared for their methacholine test outcome and its association with age, sex, diagnosis time, and disease activity.

Results: The median age was 41 (range 15 to 65) years. The median time of diagnosis was 7 (range <1 to 16) years. Forty-five percent were females, 18% had active disease and 13% had comorbidity. Nine percent of patients with UC had abnormal PFT in our study. Three cases (5%) had bronchial hyper-responsiveness that was not correlated with sex, age, time of diagnosis, or disease activity.

Conclusion: A small number of ulcerative colitis patients in our study had disturbed pulmonary function test which is in concord with the findings of other studies. However, higher rates of bronchial hyper-responsiveness have been reported in other studies. Confounding factors like cigarette smoking and medications, which were negative or minimal in our study, may influence the results.

Key words: Inflammatory bowel disease, Methacholine chloride, Bronchial hyper-reactivity

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBD) that are usually diagnosed in young ages. They seem to be the consequence of inappropriate inflammatory response in people with genetic predisposition (1). Patients with IBD usually live a long life suffering from their disease (2,3). They could be affected by other chronic diseases independently or in relation to IBD. A chronic inflammatory process could involve many different organs apart from the primary site of inflammation (4).

There are some studies in Iran showing the population and clinical characteristics of IBD to be the same as other developing countries. However, IBD's prevalence has increased during the last decades (5-7).

IBD is a multi organ disease. Extra intestinal presentations of IBD have been reported in several tissues including joints, skin, liver, and biliary system (8). However, pulmonary involvement is known to be rare. It

was first reported in 1976 (9). Pulmonary manifestations can be acute or sub-acute and could present as large or small airways, interstitial, and obstructive diseases (10).There are few population-based studies investigating the pulmonary presentation of IBD. In most cases the subclinical pulmonary involvement has no or only a few symptoms (11,12). Moreover, confounding factors like cigarette smoking or previous history of lung diseases complicate the correlation between IBD and respiratory symptoms.

Environmental factors, genetics, microorganisms, and immunological conditions are known to interact with IBD's pathogenesis (13). Similarities between small intestine and respiratory system along with their same embryonic origin are believed to cause comparable inflammatory changes in both organs (13,14). Pulmonary presentations are usually not related to the time of IBD diagnosis and in several cases have been reported in active or inactive episodes or even after colectomy (15). Medications used for IBD, sulfa drugs and immunosuppressives cause interstitial lung diseases and infections (16). Pulmonary presentations may cause bronchial hyper-responsiveness (BHR)(17). It is reported that in more than 50% of UC cases there could be disturbances in respiratory function without any clinical or pathological findings (18).

There are some studies that report a high incidence of BHR in IBD patients (12, 19). Considering the positive results of methacholine challenge test, we investigated the BHR in UC patients in an Iranian population.

MATERIALS AND METHODS

Fifty-one patients with UC referred to Shariati Gastroenterology Clinic from October 2010 to October 2011 were entered the study. An expert gastroenterologist diagnosed UC based on clinical presentation, examination, colonoscopy, radiologic and laboratory data. UC characteristics including date of diagnosis, disease activity, and presence of any comorbid conditions (uncontrolled hypertension or diabetes) were recorded.

Our exclusion criteria were cardiac attack or stroke in the previous 3 months prior to study, uncontrolled hypertension (BP>200/100 mmHg), aortic aneurysm, cigarette smoking, allergic rhinitis, COPD, infectious bronchitis, and non-compliant patients in PFT. All cases signed an informed consent form. Study protocol was approved by the "Ethics Committee of Tehran University of Medical Sciences".

Patients were referred to the Respiratory Department to carry out pulmonary function tests followed by methacholine challenge test. An expert technician did all the tests at sitting position. First, the basic forced expiratory volume in the 1st second (FEV_1) was evaluated by inhaling normal saline 0.9%. To perform the methacholine challenge test FEV_1 should have been over 70% of the predicted value. BHR was assessed by administration of increasing doses of methacholine (0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16). The test was considered positive if FEV_1 reduced by 20%, (PD20) and stopped if the methacholine dose reached 16 mg/ml.

SPSS version 16 software (SPSS Inc. Chicago, IL, USA) was used for data analysis. Categorical data were reported as number (percentage) and numeric data were reported as mean±standard deviation (SD) or median (range). Student's *t* test and Mann-Whitney test were utilized appropriately to compare data sets. P-value of <0.05 was considered statistically significant.

RESULTS

Fifty-one UC patients were included in the study from October 2010 to October 2011. General characteristics of all patients are summarized in Table 1. The average age was 43 ±14 (range 15 to 65) years. Number of males was higher. A total of 13% of cases had comorbid diseases (3 uncontrolled hypertension and 4 uncontrolled diabetes mellitus). Eighteen percent had active disease during the study.

The average results of pulmonary function test (PFT) were within normal ranges (Table 2). Clinical characteristics, PFT results, and methacholine challenge tests were evaluated for each patient. A total of 9% of patients had abnormal PFT results showing restrictive

pattern. Three patients (5%) showed positive results in methacholine challenge test (more than 20% reduction in FEV_1 in methacholine doses below 16 mg/ml, 2 cases with 8 mg/ml and 1 with 4 mg/dl of methacholine dose).

Table 1. General characteristics of all UC patients

Age Median(range)	41 (15-65)
Sex No.(%)	
Male	28 (55%)
Female	23 (45%)
Diagnosis time Median(range)	7 (<1-16)
Comorbid disease No.(%)	7 (13%)
Disease activity No.(%)	
Inactive	42 (82%)
Active	9 (18%)

Table 2. Basic PFT results, data are presented as mean± SD.

Variable	Liter	% predicted
FEV1	3.31±0.6	88±10
IVC	3.81±0.7	83±10
FEV1/IVC	-	87±7

BHR was not associated with sex, age, time of diagnosis, disease activity, and comorbidity. Pearson's correlation coefficient was not statistically significant in any cases. No significant differences were found when comparing the two groups with positive and negative methacholine test outcomes (Table 3).

Table 3. Comparison of different variables based on the methacholine challenge test outcome

Variables	Methacholine test Negative	Methacholine test Positive	P-value
Age Median(range)	41 (15-65)	60 (49-60)	0.09
Female sex No.(%)	22 (45%)	1 (33%)	1
Diagnosis time Median(range)	6 (<1-16)	6 (<1-14)	0.86
Active disease No.(%)	8 (16%)	1 (33%)	0.44
Comorbid disease No.(%)	6 (12%)	1 (33%)	0.36

DISCUSSION

A few percent of patients with UC had abnormal PFT in our study. A very small number had BHR that was not correlated with sex, age, time of diagnosis, and disease activity.

Based on severe pulmonary involvement in IBD reported in 1976 (9), it should be considered that the most frequent findings are chronic bronchitis and bronchiectasis which may not necessarily show BHR. However, Herrlinger et al. (20) found that FEV_1 and Inspiratory Vital Capacity (IVC) could decrease in significant amounts during active episodes of IBD.

It seems that in different studies small number of investigated patients had abnormal PFT. Therefore, latent pulmonary pathology should be evaluated through several methods. Karadag et al. (8) showed that while 7% of IBD patients had disturbed PFT, 26%, 50%, and 80% had abnormal findings in high resolution computed tomography (HRCT), bronchoscopy with lavage, and biopsy, respectively. Therefore, respiratory symptoms may not be clearly found but pulmonary changes are traceable through different evaluation techniques. Studies that report higher incidence of PFT abnormalities should be carefully considered to eliminate any confounding factor. Medications and cigarette smoking are two major factors affecting the lungs. In our study, smokers were excluded. Most of our patients were in remission and; therefore, the majority was not on high doses of medication. However, there are studies that have reported higher incidence of BHR (19,21) even as high as 48% (12). All the aforementioned studies were carried out with small sample sizes and none of them had excluded smokers. They also included patients with CD; positive outcome of methacholine test has been reported as high as 71% in CD (17).

Despite all the investigations about pulmonary involvement in IBD, its pathophysiology still remains unclear. Disturbed immunity regulation of intestinal epithelium antigens could systemically activate the immune cells and cause extra intestinal presentations (21).

Pulmonary pathology could be strongly related to common medications used in IBD. Sulfasalazine's side effects include pneumonitis, pulmonary infiltration and interstitial disease (17,21). Eosinophilic pneumonia is the most common side effect of sulfasalazine and mesalamine

(22). Complications could start 2 to 6 months after the initiation of therapy.

It has been reported that 3 to 8 % of the normal population may have abnormal PFT (23). Ceyhan et al. (19) could not find any significant difference between the incidence of BHR in IBD (13%) and the control group. Kullmann et al. (24) reported an 8% incidence rate for BHR in UC. Our results are in concordance with theirs. They also showed that BHR is not associated with disease activity. Other studies confirm the independence of pulmonary presentation from time of diagnosis and disease severity (19,24,25).

Interestingly, it is reported that sympathetic activity is higher in UC patients (26). Therefore, in spite of the presence of any pulmonary pathology, methacholine challenge test may not be capable of revealing that. Methacholine evaluates the cholinergic response. Increased sympathetic activity could lead to false negative results. Nutrition is also found to be important in PFT results in IBD patients (4). Patients in our study were mostly in remission phase and had a good nutritional condition that decreases the rate of abnormal PFT outcomes.

An interesting retrospective study on 2,192 patients with airway diseases for 10 years revealed that the prevalence of IBD was 4 times greater in them than in the normal population of the study (27). Since this study was conducted in a tertiary health center the possibility of referral of patients with simultaneous complications could affect the results.

In general, the incidence of pulmonary presentation was reported to be greater in other studies compared to ours (17,28). Although such differences could be attributed to population variation, exclusion of smokers and patients with the history of allergic rhinitis is also important. The contradiction in results of various studies investigating pulmonary involvement secondary to IBD, and lack of any clear presentation of pathophysiologic pathways, raise a great concern about drawing any conclusion. The influence of any confounding factor and common risk factors should be evaluated in prospective cohort studies. Considering all contradictory data available on PFT and methacholine test results in UC, these tests should not be considered alone. Pulmonary presentation should be interpreted in relation to medications used. Other diagnostic modalities, HRCT or bronchoscopy with lavage and biopsy should also be considered.

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