

Atopic Manifestations in Patients with Inflammatory Bowel Disease

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ABSTRACT

BACKGROUND: Inflammatory bowel disease, characterized by chronic relapsing immune-mediated inflammation of the gastrointestinal tract, is often associated with extra-intestinal manifestations affecting multiple organs. The aim of this study is to ascertain whether IBD is associated with atopy or not.

METHODS: The case group comprised of sixty newly diagnosed IBD patients; 51 with ulcerative colitis and 9 with Crohn's disease, whereas the control group included 60 subjects (matched for age and gender) free from any gastrointestinal symptoms. They were all subjected to full history (including pulmonary and allergic symptoms, as well as personal and family history of atopy), skin prick test, serum total IgE, pulmonary function tests, and differential leukocytic count for eosinophils. Colon biopsies for

histopathological scoring were taken from the patients.

RESULTS: IBD patients had significantly ($p < 0.05$) greater frequency of pulmonary symptoms with evident pulmonary function test (PFT) abnormalities, allergic manifestations, personal and family history of atopy, skin prick test reactivity, blood eosinophilia and increased total serum IgE levels when compared with the matched controls. However, no statistically significant ($p > 0.05$) relationship could be found between the skin prick test reactivity, serum total IgE levels and histopathological or clinical activity index.

CONCLUSION: IBD is significantly associated with atopy when compared with matched controls.

Keywords: Atopy; Inflammatory Bowel Disease; Ulcerative Colitis; Crohn's Disease; Allergy

INTRODUCTION

The term "atopy" describes the tendency to become IgE-sensitized to common allergens to which most people are exposed but do not have a prolonged IgE antibody response [1]. In most literature, atopic sensitization is defined as a positive allergen-specific serum IgE (sIgE) test or skin prick test (SPT) to any common food or inhalant allergens [2]. Atopy can be determined by skin test reactivity to environmental allergens or the detection of allergen-specific IgE in serum. The two measures have been used interchangeably to define atopy [3]. Ulcerative colitis (UC) and Crohn's disease

(CD), collectively termed inflammatory bowel disease (IBD), are complex disorders with chronic inflammation of the intestinal tract, leading to a variety of symptoms [4]. The pathogenesis of IBD seems to be more complex than one single cause and probably involves an interaction between genetic predisposing factors [5], exogenous and endogenous triggers, and modifying factors [6]. The outcome of these interactions is a spontaneously relapsing and remitting inflammatory process in intestinal mucosa associated with recruitment and activation of lymphocytes, macrophages and

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other inflammatory cells [7].

Although the primary site of involvement in IBDs is the bowel, a variety of extra-intestinal manifestations (EIMs) have been reported. The frequency of these manifestations in previous studies ranged from 21% to 41% [8]. These manifestations included many systems such as musculoskeletal, ophthalmological, dermatological and hepatobiliary tract, although virtually every organ system may be involved [9]. Atopy may be considered one of the EIMs that presents itself in different forms. The exact mechanism that links these atopic manifestations with IBD is not fully understood. Studies have indicated that Th1-related cytokines (e.g. TNF, IFN- γ , IL-12) as well as Th17-associated cytokines (e.g. IL-17A, IL-21, IL-23) are markedly increased in the inflamed mucosa of CD, whereas the cytokine profile in inflamed areas of UC exhibit increased production of the Th2 cytokines, such as IL-5 and IL-13 [10-11]. IBD patients frequently show several markers of atopy as increased tissue eosinophils [12], increased number of mast cells in intestinal tissues [13], increased serum total IgE, as well as other shared genetic defects between atopy and IBD, such as NOD1 and NOD2 [14]. The present study aims to investigate the prevalence of atopy among IBD patients by recording skin prick test reactivity, pulmonary function test abnormalities, serum total IgE and correlating these with clinical and histological activity indices. To our knowledge, no study has investigated all these parameters at once.

PATIENTS AND METHODS

Patients

This case-control study was conducted in the Department of Allergy and Clinical Immunology, Ain Shams University, Cairo between May 2010 and October 2011 after approval of the ethical review board. Sixty newly diagnosed IBD patients were enrolled; 51 with ulcerative colitis and 9 with Crohn's disease (Group A), referred to the endoscopy departments of Ain Shams, Elhussein and Cairo University hospitals. Adult patients (age range 18-60 years) with inflammatory bowel disease, who were eligible for the study, were selected based on history and clinical examination with no sex predilection. Diagnosis of IBD was confirmed by histopathological examination for colonoscopic biopsies. Another sixty control subjects, matched for age and gender (age range 22-50 years)

apparently healthy, free from any gastrointestinal or extraintestinal symptoms were selected from Ain Shams University Hospital, Egypt (Group B). Patients and controls with other medical conditions such as diabetes, hypertension and cardiac diseases were excluded.

Methods

The newly diagnosed IBD patients underwent colonoscopy, histopathological study and were classified according to the endoscopic score [15] [16], histopathological score [17] [18], extent of the disease [19], and clinical activity index [20]. Both studied groups (patients and controls) were subjected to skin prick test which was performed using common food and aeroallergen extracts. The test was read at 15-20 minutes. A wheal >3 mm in diameter was considered a positive test result for sensitization to that peculiar allergen.

The level of serum total IgE (expressed as international units per milliliter) was used as an index of atopy where optimal IgE concentration for distinguishing allergic from nonallergic individuals is approximately 100 IU/ml, measured by ELISA kit (Biocheck, Inc., Foster City, USA). Differential leukocytic count for eosinophils, and pulmonary function tests were also performed.

Pulmonary function tests were performed using a computer-assisted spirometer. FEV1, FVC, and FEV1/FVC ratio were recorded. Results were interpreted as: normal (FEV1/FVC \geq 70% and FVC \geq 80% predicted), restrictive (FEV1/FVC \geq 70% and FVC < 80% predicted), or obstructive (FEV1/FVC < 70% independent of FVC values).

Statistical Methodology

Statistical analysis of data was done using Statistical Package for Social Sciences version 13 for Windows (SPSS Corp., USA). Chi-square test was used to compare qualitative variables between groups. Unpaired t-test was used to compare two groups as regard to quantitative variables in parametric data. For all tests, a p (probability) value < 0.05 was considered significant and a p-value < 0.01 was considered as highly significant.

RESULTS

The clinical and laboratory characteristics of patients and controls are summarized in Table 1. Demographic data of both groups showed no statistically significant difference with p-values 0.118, 0.361 for age and sex, respectively. Nine

	Subjects	Controls	p-value
Age (years)	35.02 ± 11.67	33.62 ± 6.85	0.118
Sex			
MALE	31	26	0.361
FEMALE	9	34	
Pulmonary symptoms	16/60	7/60	0.037
Allergic symptoms	19/60	9/60	0.029
Extraintestinal manifestations	9/60		
Skin prick test reactivity	19/60	5/60	0.001
High serum total IgE	30/60	6/60	<0.001
Pulmonary function tests abnormalities	13/60	5/60	0.041

Table 1: Clinical and laboratory characteristics of the IBD patients and controls (means ± SD)

of the 60 IBD (15%) patients had a previous history of EIMs such as arthritis and pyoderma gangrenosum. Pulmonary and allergic symptoms (for more than 6 months) were significantly more common among IBD patients than control subjects with p-values 0.04 and 0.03, respectively. Twelve (20%) patients had asthma, 7 (11.7%) patients reported allergic urticaria and 6 (10%) patients suffered from allergic rhinitis. Positive skin prick test and high serum total IgE values were more common among IBD patients than control subjects (p-values 0.001 and <0.001, respectively). There was statistically significant increase in pulmonary function test abnormalities in Group A compared to Group B (8 in Group A vs. 3 in Group B obstructive, 1 in Group A vs. 1 in Group B restrictive and 4 in Group A vs. 1 in Group B small airway affection pattern) by using chi-square test with p-value 0.04.

When relating skin prick test reactivity and serum total IgE to histopathological activity index (mild, moderate and severe), there was no

statistically significant relation with p-values 0.20, 0.87 respectively as shown in Table 2. The same insignificant relationship was found when relating these two parameters to clinical activity index (mild, moderate and severe), with p-values 0.80, 0.44 respectively as shown in Table 3.

DISCUSSION

Several studies have investigated atopy in IBD patients. Most studies [21-24], but not all [25, 26] have reported an increased prevalence of atopic eczema in patients with IBD. With respect to the incidence of other disorders, such as bronchial asthma, allergic rhinitis, and hay fever, results have been variable.

Our study was conducted on two groups; sixty newly diagnosed IBD patients versus another sixty matched controls (all free from any gastrointestinal symptoms; nevertheless presence or absence of atopic and respiratory symptoms was not a determining factor for their selection).

Both studied groups were comparable regarding demographic data. Pulmonary symptoms (cough, expectoration, dyspnea and wheezes) were more common among IBD patients, and this is in agreement with a number of previous reports, indicating that the respiratory system is involved in IBD [27]. Among 44 randomly selected IBD patients, Douglas et al., [28] found that 48% had unspecified respiratory symptoms. Songur et al., [29] found that 16 of 36 IBD patients (44%) in a gastroenterology clinic had symptoms of wheezing, cough, sputum production, or breathlessness. Ceyhan et al., [30] found that 15 of 30 consecutively surveyed IBD patients had symptoms of dyspnea, cough, sputum production, or wheezing for more than a month.

Our results found high prevalence of atopy and allergic diseases in IBD patients, with asthma as the most common atopic feature. The finding that atopic eczema was more common in CD was reported earlier by Pugh et al., [31] in 200 patients, while all kinds of atopic diseases were more common in patients with UC (n = 300).

Louis and colleagues [34] found that the proportion of atopy tends to be higher in IBD group than in control group ($p < 0.10$). Atopy, defined by skin prick test, was more common in IBD patients (42%) than in controls (21%). There were several positive reactions in these subjects. Sixteen out of 38 IBD patients had at least one positive reaction with the prick test, including the 11 with history of atopy. This is in line with our study where 19 out of 60 IBD patients had at least one positive reaction with the prick test and 18 of them were reactive to more than one aeroallergen.

The above observations, have led several groups to conduct allergologic studies in IBD patients. D'Arienzo et al., [35] studied total serum IgE and eosinophils in the intestinal mucosa of fifty UC patients compared to another 50 healthy subjects. IgE levels were higher in UC patients than in controls ($p = 0.02$). The degree of colonic tissue eosinophilia was higher in the presence of skin reactivity to food allergens. Thus, UC patients frequently show several markers of allergy suggesting an association between UC, tissue eosinophilia, and type-I allergy. In the same study, a higher prevalence of allergic symptoms was found in patients (56%) and their first-degree relatives (52%) than in controls (18% and 26%) ($P < 0.0001$; $P = 0.008$).

Serum total IgE levels were high in our IBD patients with highly significant difference ($p < 0.001$) compared to controls. However, no statistical difference was reported regarding

serum eosinophils.

Levo et al., [36] showed that serum concentration of IgE, as well as the prevalence of patients with "high IgE" was significantly increased in IBD. Among patients with IBD, those with Crohn's disease or those in relapse had the highest levels of IgE. In contrast, other studies have shown conflicting results regarding possible association between IBD and atopic diseases [37].

Impaired pulmonary function tests were found in 21.7% of our subjects in comparison with 8.3% of the controls. Similarly, Godet et al., [38] also detected spirometric abnormalities in 55% of the patients with UC; 15/66 subjects had an obstructive pattern, 19/66 had abnormal diffusion, 1/66 had a restrictive pattern and 5 subjects had both an obstructive pattern and abnormal diffusion. Abnormal pulmonary function could not be predicted by the current or past smoking status, family history of respiratory diseases, occupational history or current medication. Furthermore, similar findings were also detected by Ceyhan and colleagues [30]. Interestingly, Munck et al., [39] found no obstructive pattern in children in the active phase and remission of Crohn's disease. However, our study included only adult patients.

The predominance of Th2 cytokines in cases of ulcerative colitis [40] may provide an explanation for the atopic manifestations associated with it and IL17 may provide an explanation for the atopic manifestations associated with both CD and UC.

LIMITATIONS OF THIS STUDY

The small sample size is a limitation of this study. Limitations also include studying atopy in both ulcerative colitis and Crohn's disease as one entity and measuring blood eosinophils rather than tissue eosinophils in the intestine.

CONCLUSION

Atopic manifestations are more prevalent in patients with IBD than in control subjects as shown by skin prick test reactivity to various food and aeroallergens, high levels of serum total IgE, and abnormal pulmonary function tests.

Future research utilizing large scale randomized controlled studies is required to examine the role of immunotherapy for inhalant allergens or diet elimination of food allergens in atopic IBD patients in improving intestinal symptoms and decreasing frequency of relapses, and to investigate new therapeutic perspectives in the treatment of both atopy and IBD as anti-IgE antibody.

Histological activity index of IBD patients				
	Mild	Moderate	Severe	p-value
Number of patients	11	21	28	
Positive skin prick test	6(10%)	5(8.3%)	8(13.3%)	0.201
High serum total IgE	6(10%)	11(18.3%)	13(21.7%)	0.869

Table 2: Relation between histological activity index of IBD patients and skin prick test reactivity and high serum total IgE

Clinical activity index of IBD patients				
	Mild	Moderate	Severe	p-value
Number of patients	11	20	29	
Positive skin prick test	4(6.7%)	7(11.7%)	8(13.3%)	0.803
High serum total IgE	5(8.3%)	11(18.3%)	14(23.4%)	0.438

Table 3: Relation between clinical activity index of IBD patients and skin prick test reactivity and high serum total IgE

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