ORIGINAL ARTICLE

Association of Food Allergies, Cow's Milk Allergy, and Asthma With Pediatric Inflammatory Bowel Disease

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Abstract- There are controversies on the association of childhood allergic diseases with inflammatory bowel diseases (IBD). The aim of this study was to examine the association between food allergy, cow's milk allergy (CMA), and asthma with pediatric IBD in Iranian population. This case-control study was conducted on 200 individuals less than 18-year-old (100 with IBD and 100 as control group). Medical records, clinical presentation, and laboratory and para-clinical findings related to food allergy, CMA, and asthma were reviewed for all participants in both groups and were recorded. Among 100 children with IBD, 40 had Crohn's disease, and 60 had ulcerative colitis. The frequency of food allergy, cow's milk allergy, and asthma in children with IBD was significantly higher than the control group (P<0.001). Asthma in children with Crohn's disease was significantly more prevalent than children with ulcerative colitis (P=0.008). Food allergy (OR: 22.1, 95% CI: 5.1-95.05, P<0.001), CMA (OR: 15, 95% CI: 3-67, P<0.001), and asthma (OR: 10, 95% CI: 3-37.05, P<0.001) were significantly associated with increased risk of IBD in children. Food allergy, CMA in infancy and asthma are more prevalent in children with different subtypes of IBD. The diagnosis of these risk factors is associated with increased risk of Crohn's disease and ulcerative colitis.

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Keywords: Asthma; Child; Crohn disease; Food hypersensitivity; Milk hypersensitivity; Ulcerative colitis

Introduction

Although inflammatory bowel diseases (IBD) is reported to be relatively more prevalent in Northern and Western Europe as well as North America (1,2), recent studies show a gradually increasing rate of IBD in many developing countries in Africa, South America, and Asia (3,4). The incidence and prevalence of IBD in pediatric populations in Iran is still unclear. However, according to recent studies, it appears that neither UC nor Crohn's disease is rare in Iran. Indeed their incidence appears to have increased during the recent years (5).

Etiology of IBD including ulcerative colitis, Crohn's disease, and indeterminate colitis is uncertain and may be due to interactions between various immunologic, environmental, and genetic factors (6). Improvements in general health and hygiene have been incriminated as a significant contributor to the growing incidence of IBD

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globally (5).

The increase in allergic disease together with the process of westernization is considered to reflect changes in the socioeconomic environment; however, it is not clear whether childhood allergic disease involves the pathogenesis of IBD (6). In Virta *et al*., study in Finland, cow's milk allergy (CMA) in infancy was a risk factor of pediatric IBD and asthma was a risk factor of Crohn disease (7). Imanzadeh *et al*., in a cross-sectional study found that food allergy was frequent in Iranian pediatric IBD patients (8). Lack of enough evidence for the contribution of allergic diseases in the etiology of IBD stimulated our interest in examining the association between food allergy, CMA, and asthma with pediatric IBD in Iranian population.

Materials and Methods

This case-control study was conducted on 200 subjects less than 18-year-old (100 with IBD and 100 as control group) referred to the Children's Medical Center - the main tertiary referral center of pediatric diseases- in Tehran, Iran from January 2014 to March 2015. The study was approved by the ethics committee of School of Medicine in Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1395.1763). Written informed consent was taken from both parents and participants.

The diagnosis of IBD was verified based on well-established clinical, radiologic, endoscopic, histological, and surgical criteria (9,10) in the opinion of a pediatric gastroenterologist. Subtypes of IBD diagnosis (International Classification of Disease-10 codes K 50 or K 51) were considered for 100 patients of the case group. IBD was classified as Crohn's disease and ulcerative colitis. For each patient with diagnosis of IBD, one eligible control child was randomly selected from children without organic diseases and was individually matched for date of birth and place of residence. Demographics were self-reported in the questionnaire given to the participants.

Medical records, clinical presentation, and laboratory and paraclinical findings related to food allergy, CMA, and asthma were reviewed for all participants in both groups and were recorded. All data on which the reimbursement for food allergy, CMA and /or asthma became effective was extracted.

Food allergy and CMA (K 52.2, L 27.2) were diagnosed according to a written certificate including the diagnostic criteria and were evaluated by a pediatric gastroenterologist and a pediatric allergist. For food allergy, the criteria included skin tests (prick and patch), Rast test, and elimination diet (11,12). For CMA, the criteria included clinical observations and milk elimination, but double-blind testing was not preformed (11,13).

The diagnosis of asthma (ICD-10 codes j 45) was verified based on diagnostic spirometry in the opinion of a pediatric pulmonologist or allergist for children above 6 years old. For less than 6 years old children, asthma was identified based on the sum of historical, clinical, and laboratory findings (14).

Data were recorded as mean±standard deviation (SD) or number (percent) where appropriate. Categorical variables were analyzed using Chi-square test. The associations of food allergy, CMA, and asthma with the risk of IBD, Crohn's disease, and ulcerative colitis were analyzed using conditional logistic regression analysis. The strengths of the associations were assessed using odds ratios with 95% confidence intervals (95% CI). *P* less than 0.05 were considered as significant.

Results

Among 100 children with IBD, 40 had Crohn's disease, and 60 had ulcerative colitis. Mean age at IBD diagnosis was 8.0±3.7 in the case group (8.2±4.2 in participants with Crohn's disease and 7.9±3.4 in participants with ulcerative colitis). Characteristics of food allergy, cow milk allergy, and asthma in children with IBD and control group are shown in table 1. The frequency of food allergy, cow milk allergy, and asthma in children with IBD was significantly higher than the control group ($P<0.001$). Food allergy and cow milk allergy in children with ulcerative colitis was more prevalent than children with Crohn's disease, but the difference was not statistically significant ($P=0.378$, $P=0.149$). Asthma in children with Crohn's disease was significantly more prevalent than children with ulcerative colitis ($P=0.008$).

Association of food allergy, cow milk allergy, and asthma with IBD in children has been shown in table 2. Food allergy, CMA, and asthma were significantly associated with increased risk of IBD in children. In subgroup analysis, food allergy, CMA, and asthma were significantly associated with increased risk of Crohn's disease, but only asthma was not associated with ulcerative colitis.

Table 1. Characteristics of food allergy, cow's milk allergy, and asthma in children with IBD and control group

		Case group			Control group (N=100)
		Total (N=100)	Crohn's disease (N=40)	Ulcerative colitis (N=60)	
Food Allergy	**Frequency** [a]	31 (31)	10 (25)	21 (35)	2 (2)
	Age at diagnosis (year)[b]	1.4±1.0	2.5±3.7	1.4±1.2	1±0
Cow's Milk Allergy	**Frequency** [a]	24 (24)	6 (15)	18 (30)	2 (2)
	Age at diagnosis (year)[b]	1±0.2	1±0	1±0.2	1±0
Asthma	**Frequency** [a]	25 (25)	16 (40)	9 (15)	3(3)
	Age at diagnosis (year)[b]	4.4±3.4	4.2±3.8	4.8±2.6	7±0

[a] Data are presented as number (percent); [b] Data are presented as mean±SD

Table 2. Association of food allergy, cow's milk allergy, and asthma with IBD in children

		Crude			Adjusted*		
		0R	95%CI	*P*	0R	95%CI	*P*
IBD	**Food Allergy**	22.1	5.1-95.05	<0.001	54.01	10.01-291	<0.001
	Cow's Milk Allergy	15	3-67	<0.001	47	8-260	<0.001
	Asthma	10	3-37.05	<0.001	7	1.1-30.00	<0.001
Crohn's disease	**Food Allergy**	16	3-78	<0.001	38	6-228	<0.001
	Cow's Milk Allergy	8	1.05-44	0.001	24	3-156	<0.001
	Asthma	21	5-80.01	<0.001	14	3-62	<0.001
Ulcerative colitis	**Food Allergy**	26	5-117	<0.001	69	12-398	<0.001
	Cow's Milk Allergy	20	4-94	<0.001	78	13.09-466	<0.001
	Asthma	5	1-22	0.001	3	0.01-16	0.87

* Adjusted for age, sex, and place of residence

Discussion

The contribution of allergy, if any, to the development of IBD has long been a matter of debate. In 1968, Hammer *et al*. hypothesized the familial susceptibility for IBD and found a greater prevalence of allergic diseases including eczema and hay fever in patients with Crohn's disease, ulcerative colitis, and their first-degree relatives than the matched controls (15). The results of studies on the association of IgE level and IBD are inconsistent (16-18). There was no difference between controls and IBD patients, or IBD subgroups in terms of serum IgE levels in Troncone *et al*., and Ceyhan *et al*., studies (16,18) while raised levels of serum IgE in patients with IBD was reported in Levo *et al*., study (17). However, most studies in this field are on adult populations, and studies on the pediatric IBD are limited. Therefore, the present study focused on the association of food allergy and asthma with pediatric-onset IBD in Iranian children.

In the present study, the frequency of food allergy in children with IBD was significantly higher than the control group, and food allergy was associated with increased risk of IBD. In another study by Cai *et al*., (14) serum food-specific antibodies were assessed in 112 patients with IBD and compared with healthy controls (19). Serum IgG levels in patients with IBD were significantly higher than the control group. There

was no difference between patients with Crohn's disease and ulcerative colitis in terms of serum IgG antibodies (19). Although there is evidence that adverse reaction to food may induce intestinal inflammation and result in intestinal bleeding, especially in infants (20), its effect on chronic intestinal inflammation is not known.

The frequency of cow milk allergy in children with IBD was significantly higher than the control group in the present study and asthma was associated with increased risk of IBD. Virta *et al*., previously reported that CMA in infancy was associated with 1.92 times increased the risk of Crohn's disease and 1.71 times increased the risk of ulcerative colitis in Finnish children (7). Glassman *et al*., in a study on 78 patients with IBD and 36 control children found that CMA during infancy in children with ulcerative colitis (20.9%) was significantly higher than children with Crohn's disease (8.5%) and the control group (2.8%) (21). In Lerner *et al*., study, young patients with Crohn's disease had higher IgG antibodies against bovine serum albumin and beta-lactoglobulin A and B than patients with ulcerative colitis and the control group (22).

In the present study, the frequency of asthma in children with IBD was significantly higher than the control group, and asthma was associated with increased risk of IBD. The link between airway diseases and IBD has suggested four decades ago for the first time (23). In Virta *et al*., study on Finnish children, childhood asthma was only associated with 2.33 times increased the risk of Crohn's disease (7). In a population-based cohort on 8072 patients with IBD, asthma was the second most prevalent comorbidity in both Crohn's disease and ulcerative colitis (24). In a study on 30 Turkish patients, allergic and respiratory symptoms, abnormal lung function, and positive skin prick test were more prevalent in patients with IBD compared to the control group (18). Vutcovici *et al*., believe that there is a two-way association between IBD occurrence and airway diseases (25).

Prevalence of asthma in children with Crohn's disease was significantly higher than children with ulcerative colitis in the present study that is consistent with previous studies in the adult population (6,24,26,27). Bernstein *et al*., also found that asthma was the most common comorbidity in patients with Crohn's disease (24).

The limitation of the present study was its small sample size in the case group. However, it should be noted that pediatric-onset IBD is not prevalent in Asia and Iran. As strength, the diagnosis of IBD, food allergy, CMA, and asthma was based on written certificates by specialist that decreases the possibility of misdiagnoses. Another strength is that CMA was studied as an independent risk factor in addition to food allergy.

In conclusion, food allergy, CMA in infancy and asthma are more prevalent in children with different subtypes of IBD. The diagnosis of these risk factors is associated with increased risk of Crohn's disease and ulcerative colitis. The mechanisms of these associations are still unclear. More studies with large and register-based sample size are needed to understand the association of IBD with food allergy, CMA, and asthma and related mechanisms.

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