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ORIGINAL ARTICLE



IgE-sensitization to food and inhalant allergens in IBD patients compared with normal blood donors at Oslo University Hospital, Norway

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ABSTRACT

Objectives: Crohn's disease (CD) and ulcerative colitis (UC) have been regarded as autoimmune Th-1/Th-17- and Th-2-associated conditions, respectively. The aim of the study was to examine possible differences in allergen sensitization between these diseases and relative to normal blood donors (BD).

Materials and methods: Plasma from 29 UC and 37 CD patients with moderate disease activity and 100 healthy age- and gender-matched BD, were analyzed for specific IgE to 22 food- and 28 inhalation allergens using EUROLINE atopy screen.

Results: There was significantly higher proportion of allergen sensitized patients in UC compared to BD. Corresponding mean percentages for UC, CD and BD were 8.5, 8.9 ($p = .2$) and 5.9 ($p = .04$). There was no intergroup difference in sensitization to food allergens. Most prominent result was the double level of sensitization to inhalants in CD (15%) compared to BD (8%) ($p = .03$). Overall highest levels of sensitization to inhalants were for grass pollens. Interestingly, the number of allergens ($n = 50$) the subjects were sensitized to, was significantly lower among UC ($n = 20$; 40%) ($p = .0005$) than CD ($n = 31$; 62%) and BD ($n = 38$; 76%).

Conclusions: The percentage of individuals sensitized to inhalants in CD and to inhalants and foods in UC, were higher than corresponding results in BD. However, whereas allergen positive reactions in CD were comparable to those in BD, they were reduced in UC because of the few UC reactions to food allergens. This contrasts previous data and the study also points to sensitization to inhalants as a potential factor in the complex pathogenesis of IBD.

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CD; UC; BD; inhalation allergens; food allergens

Introduction

Previously, the inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) have been considered as conditions that are T helper (Th)-1 and Th-17, and Th-2 associated, respectively [1].

The evidence is strengthened for Th-1 and Th-17 responses being pathogenic for CD [2,3]. However, although Th-2 responses play a pathogenic role in experimental murine colitis models, negative outcomes in clinical trials with anti-IL 13 therapy support absence of role for Th2 response in ulcerative colitis [4]. Among these three major types of cell-mediated effector immunity, Th-1 normally protects against intracellular pathogens and tumor development, Th-2 against helminthes and rejection (during pregnancy), and Th-17 against extracellular pathogens [5]. Whereas the first and third type of immunity may promote autoimmune disease such as CD when overreacting, the second type, Th-2, can cause allergy [5]. In IBD, IgE sensitivity to food allergens would be of special interest and could be compared to that of healthy blood donors, who are often used as normal controls. A recent meta-analysis has reported [6] a similar co-occurrence of asthma with CD and UC. In a study from 1979 of 500 IBD patients [7] there also was an increased

occurrence of allergic rhinitis and eczema in UC, whilst only eczema was increased in CD. Moreover, increased IgE sensitization to twelve food allergens, both in UC and CD, has been demonstrated in two studies [8,9], indicating that more and broader studies of this kind could be of interest.

The aim of this study was to examine whether there was i) more IgE-sensitization to inhalant and food allergens among IBD patients than in normal blood donors and ii) a difference in allergen sensitization profiles and if so, whether this difference is significant between UC and CD patients. Allergen sensitization in the serum material was analyzed by Euroimmun's extensive repertoire for specific IgE testing.

Materials and methods

Materials were heparin plasma from 29 UC and 37 CD patients at Oslo University Hospital (OUH) who were controls (given placebo for 2 weeks) in a clinical intervention study with an anti-inflammatory mushroom extract (AndosanTM) as add-on oral treatment [10,11]. During 2012–14 blood samples from the 37 CD patients were collected in January (16.2%), February (2.7%), March (16.2%), May (10.8%), June (8.1%), August (8.1%), September (16.2%), October (2.7%) and November (18.9%). During 2013–14 blood samples from the

29 UC patients were collected in January (10.3%), February ($n=5$; 17.2%), March ($n=11$; 37.9%), May ($n=3$; 10.3%), September ($n=3$; 10.3%) and October (13.8%). Accordingly, more than half of the patients, 56.7% in CD and 51.6% in UC, had blood samples taken outside of the conventional season for airborne allergy. The median age of the CD patients was 42 years (range 23–74 years) of whom 14 were men and 23 women. Corresponding numbers for the UC patients were 37.5 years (range 23–67 years) and 14 and 15, respectively. In CD these patients had a symptom score of at least 3 defined by the simple CD activity index (SCDAI) [12], of whom they mostly had mild (score 3–5) but also moderate disease (score 6–9). In patients with UC [10] a modified version of the clinical activity index (CAI) (score 1–15) was used [13]. Patients with score ≥ 3 were included in this study and the severity of disease was similar to that of the CD patients. More characteristics of the IBD patients are shown in these publications [10,11]. The current IBD patients given placebo are further in this study solely named as CD or UC patients, respectively. In addition, heparin plasma from 100 consecutive normal blood donors (BD), 50 males and 50 females, with median age (range) 42.5 (20–67) and 43.5 (20–69) years, respectively, was collected during the pollen season in mid-April of 2015.

Specific IgE against 50 allergen extracts and cross-reactive carbohydrate determinants (CCD) that is present in many plant and animal allergens, was measured using the EUROLINE atopy screen immunoblot (DQ-3790, Euroimmun AG, Germany). The 50 natural allergens could be divided into 28 food components (tomato, carrot, potato, celery, egg white, egg yolk, cow's milk, codfish, crab, shrimp/prawn, bovine serum albumin, alpha-lactalbumin, beta-lactoglobulin, casein, beef, mutton/lamb, baker's yeast, wheat flour, rye flour, rice, soybean, sesame, peanut, hazelnut, almond, apple, kiwi, apricot) and 22 inhalation components of tree pollen (alder, birch, hazel, oak, cypress), weed pollen (common ragweed, mug worth, English plantain), grass pollen (sweet vernal grass, orchard grass, timothy grass, cultivated rye), molds (*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria alternata*), animals (cat, dog, horse) and house dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, house dust). Each immunoblot contained 10 membrane chips and comprised the listed allergen extracts. Immunoblot incubation was performed manually according to the manufacturer's instructions. Briefly, the test strips were incubated with a 1:11 dilution of the patient's plasma at room temperature for 60 min. Subsequently, IgE was detected by incubation with an anti-human IgE antibody conjugated with alkaline phosphatase for 60 min at room temperature, followed by incubation with chromogenic substrate NBT/BCIP for 10 min at room temperature. Finally, the reaction was stopped with distilled water. The IgE test was automatically evaluated using the EUROLIneScan software (Euroimmun AG, Germany). Specific IgE results were expressed in EAST-classes 0–6. A result $\geq$ class 1 was considered positive for the presence of allergen-specific IgE in the plasma.

As the data did not pass the normality test Mann-Whitney test was used for comparison between groups of sum of all positive reactions for all allergen specificities given as

slgE $\geq$ EAST class 1 in the Euroline Atopy Screen. Fischer's exact test was used for comparison of group wise proportion of allergen sensitization. p Values $< .05$ were considered statistically significant and P values around 0.1 indicative for a trend.

The study was approved by the regional ethical committee (2011/404-8 South-East (D) Norway).

Results

Among 66 IBD patients (37 CD and 29 UC) (Figure 1(a,b)) and 100 normal blood donors (Figure 1(c)) at Oslo University Hospital, 44% and 47%, respectively, had positive reactivity (EAST class ≥ 1) against one or more of the 50 allergens tested for with the Euroline Atopy Screen (Table 1).

Out of 50 allergens the number that the subjects were sensitized to was 38 (76%) for BD versus 31 (62%) for CD ($p=.19$) and 20 (40%) for UC ($p=.0005$). The distribution of type of allergen that provoked sensitization in the CD, UC and BD groups, is shown in Figure 1(a,b,c), respectively. Of special notice is the significantly lower number of food allergens giving reactions ($n=4$) in the UC patients ($p=.0002$) compared with in CD ($n=17$) and in BD ($n=17$). For inhalation allergens there also was a reduction of allergens giving sensitization in the CD group ($n=14$) compared with the BD ($n=21$) ($p=.02$).

Group-wise calculation of the average percentage $\pm$ SD of all allergen positive reactions, resulted in 8.8 ± 7.4 for IBD patients and 5.9 ± 5.1 for the BD ($p=.06$). When UC and CD were compared versus BD for the two groups of sensitized allergens (Table 1), the percentage was significantly higher only for the UC group (8.5 vs 5.9). However, when comparing CD versus BD there was an increase of inhalation allergens (14.8 vs 8.0) but not for food allergens (3.4 vs 4.1) in the former group. Four out of the five inhalation allergens that were detected in the highest proportion of individuals in the three groups were identical; orchard grass, sweet vernal grass, timothy grass and cultivated rye.

Discussion

Although healthy BD were sensitized for a higher number of allergens than UC and CD patients, the two main findings in this study was that the percentage of sensitized individuals was higher in the IBD groups; in UC with regard to all allergens (food and inhalation) and in CD for inhalation allergens.

The higher frequency of specific allergen sensitization for inhalation allergens in CD patients relative to both UC patients and normal controls contrasts the dogma that CD is regarded as a Th-1 induced disease.

CD patients have been shown to have elevated levels of antibody to *Mycobacterium avium* subsp. *paratuberculosis* [14], which may indicate that CD patients have a weaker immune defense against intracellular microbes than do UC patients or healthy individuals. Since it has also been found that tuberculosis patients have more allergy than their tuberculosis-free controls [15], this probably also applies to paratuberculosis. Hence, CD patients were expected to be more

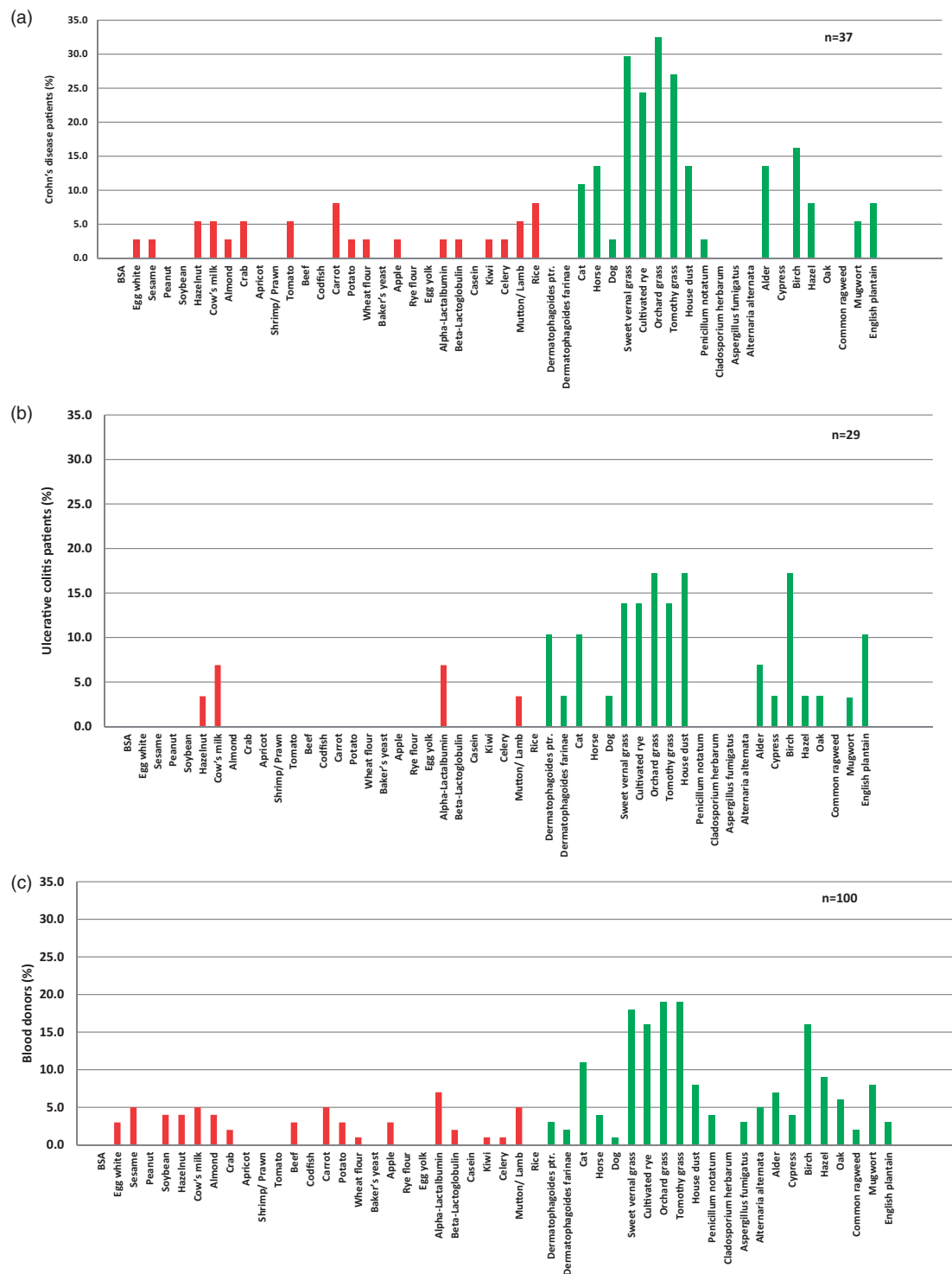


Figure 1. Distribution of positive reactivity (EAST class ≥ 1) in % against one or more of the allergens with the Euroline Atopy Screening among CD (a) and UC (b) patients and normal BD (c) Food allergens (egg white to rice) are listed to the left, followed by inhalants. IgE-sensitization specificities are shown for CD (Fig. 1a), UC (Fig. 1b) and for BD (Fig. 1c).

sensitized to allergens than UC patients. This is in accordance with our current finding, since the increased sensitization to inhalants in CD was most remarkable (Table 1). However, the lack of increased sensitization to 22 food allergens in this study in IBD-patients relative to healthy controls was in contrast to studies on 12 similar antigens. More specifically, in one study [8] the specific IgE response was more pronounced in UC than CD and *vice versa* in the other study [9]. In the current study, the percentages for sensitivity to food allergens

were all-over more than two-fold lower than the sensitization to inhalants (Table 1), which were the cause for the significant results found in CD and UC compared with healthy individuals. Interestingly, four out of the five inhalants (variants of grass and rye) affecting most individuals were in common for the BD, UC and CD groups, which may imply that high degree of such sensitization is harmful for IBD patients.

The current study demonstrated that patients with CD had increased sensitization to inhalants, and did not support

Table 1. Percent allergen sensitization quantification response (Σ EURO class 1–5/# pos) in BD ($n = 100$) and patients with CD ($n = 29$) and UC ($n = 37$).

Sensitization to allergens	Percent ($\pm$ SD) sensitization response (no. of allergens)			Comparison	p value
	BD	CD	UC		
General ($n = 50$)	5.9 $\pm$ 5.1 ($n = 38$)	8.9 $\pm$ 8.5 ($n = 29$)	8.5 $\pm$ 5.3 ($n = 20$)	BD vs CD	0.20
				BD vs UC	0.04
				CD vs UC	0.20
Food ($n = 28$)	3.4 $\pm$ 1.6 ($n = 17$)	4.1 $\pm$ 1.9 ($n = 17$)	5.1 $\pm$ 2.0 ($n = 4$)	BD vs CD	0.50
				BD vs UC	0.16
				CD vs UC	0.13
Inhalation (22)	8.0 $\pm$ 6.0 ($n = 21$)	14.8 $\pm$ 9.8 ($n = 14$)	9.4 $\pm$ 5.5 ($n = 16$)	BD vs CD	0.03
				BD vs UC	0.43
				CD vs UC	0.30

that CD or UC were afflicted with any enhanced reactivity towards food allergens. Interestingly, the levels of enhanced inhalants were similar irrespective of belonging to the groups of IBD patients or blood donors. This finding contributes to increased knowledge about this complex disease. However, the controversy regarding increased allergen sensitivity in CD patients must prompt larger studies to verify these results. If so, the role of cell-mediated effector immunity in IBD is still to be debated.

Analysis of specific IgE to inhalant and food extracts does not allow to determine the extent of primary IgE sensitization to plant food allergens (fruits, nuts etc.) compared to cross-reacting IgE antibodies mounted against pollen allergens (so called pollen-fruit syndrome). This differentiation can be done exclusively by using allergen component-based diagnostics, also called molecular allergologic diagnostics, which would be of great interest but is beyond the scope of our study.

Conclusions

In this study with inclusion of hitherto more food allergens than previously examined, a major result was that the number of allergens provoking sensitization as well as percentage of sensitized individuals was either similar (CD) or reduced (UC) as compared with healthy BD, thereby contrasting previous data. On the other hand, the levels of inhalants in CD and combined with food allergens in UC, respectively, were higher than corresponding results for the group of BD. Accordingly, this study pointed to increased levels of inhalation allergens as a potential source in the presumably multifaceted pathogenesis of inflammatory bowel disease.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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